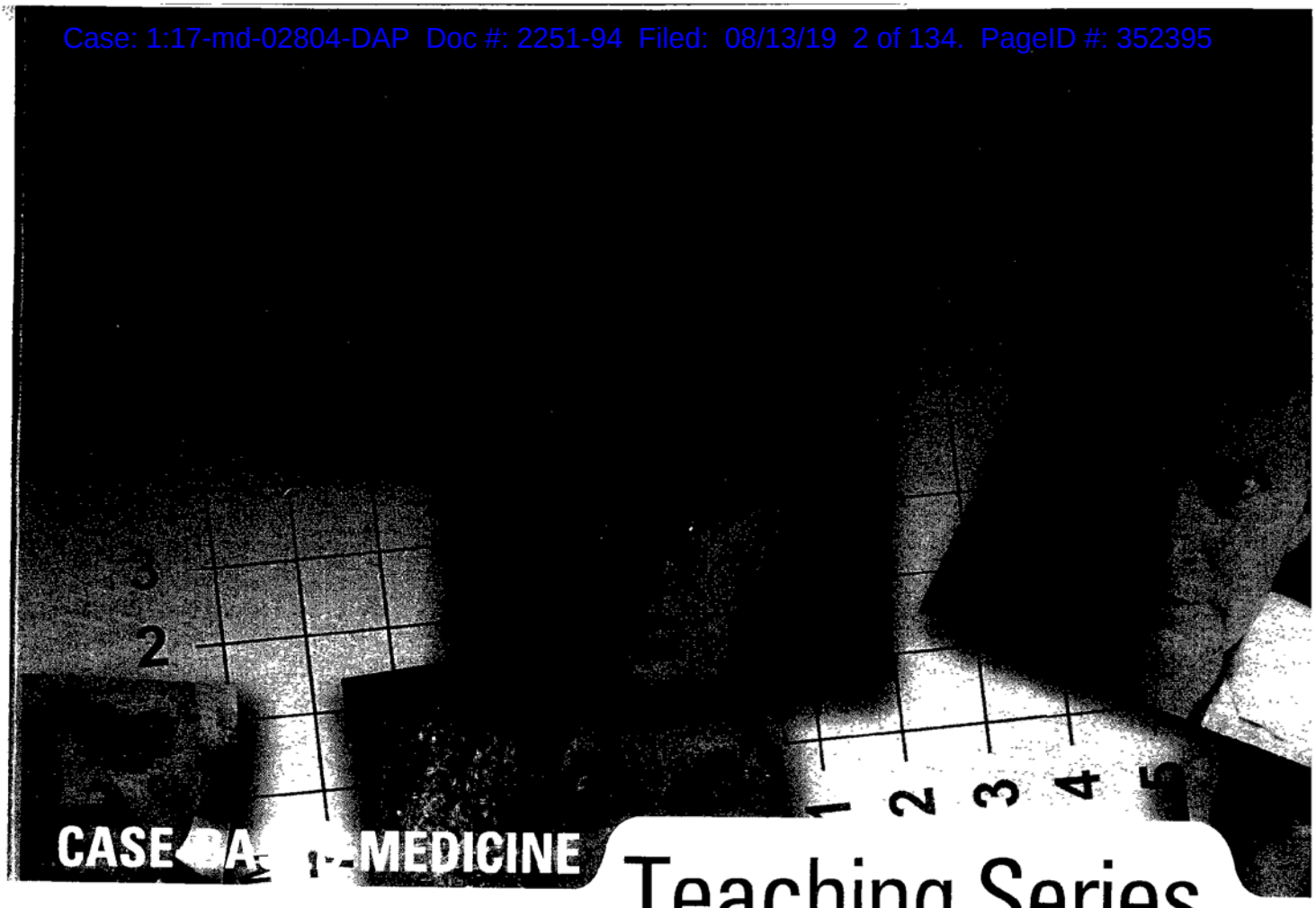
EXHIBIT 94



CASE [illegible] MEDICINE

Teaching Series

Continuing Medical Education

Persistent and Breakthrough Pain

Steven P. Cohen, MD
Course Director

Perry G. Fine, MD
Faculty Editor

Release date: June 30, 2008
Expiration date: June 30, 2009

Jointly presented by The Johns Hopkins University School of Medicine and Advanced Strategies in Medicine

JOHNS HOPKINS MEDICINE
CONTINUING MEDICAL EDUCATION

ADVANCED STRATEGIES IN MEDICINE
A McMahon Group Company

Supported by an educational grant from **Cephalon, Inc.**

Persistent and Breakthrough Pain

Course Director
Steven P. Cohen, MD

Associate Professor of Anesthesiology and Critical Care Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Faculty Editor
Perry G. Fine, MD

Professor of Anesthesiology
Pain Research Center
University of Utah School of Medicine
Salt Lake City, Utah

Jointly presented by The Johns Hopkins University School of Medicine and Advanced Strategies in Medicine

Supported by an educational grant from Cephalon, Inc.

Release Date: June 30, 2008
Expiration Date: June 30, 2009

Case-Based Medicine Teaching Series

McMahon Group
New York, NY

Typeset by Max Graphics, New York City

Printed in the U S A

Persistent and Breakthrough Pain

Table of Contents

CME Preamble

Persistent and Breakthrough Pain

Jointly presented by The Johns Hopkins University School of Medicine and Advanced Strategies in Medicine

Date of Release: June 30, 2008
Date of Expiration: June 30, 2009
Estimated Time To Complete This Educational Activity: This activity should take approximately 3 hours to complete.

COURSE DIRECTOR

Steven P. Cohen, MD
Associate Professor of Anesthesiology and Critical Care Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland

FACULTY EDITOR

Perry G. Fine, MD
Professor of Anesthesiology
Pain Research Center
University of Utah School of Medicine
Salt Lake City, Utah

FACULTY REVIEWERS

Charles E. Argoff, MD
Professor of Neurology
Albany Medical College
Director, Comprehensive Pain Program
Albany Medical Center
Albany, New York

Michael J. Brennan, MD
The Pain Center of Fairfield
Fairfield, Connecticut
Senior Attending Physician
Department of Medicine, Physical Medicine, and Rehabilitation
Bridgeport Hospital
Bridgeport, Connecticut

Statement of Need

Chronic pain is a common and serious condition, detrimental to patient function and quality of life. Because pain has many causes, a careful differential diagnosis is needed to identify underlying disorders and develop a therapeutic plan. This is made more difficult by the complex nature of chronic pain, which often has 2 components—baseline persistent pain and breakthrough pain (BTP)—that must be independently assessed and treated. In particular, this requires that treatment be tailored to the individual patient, with the goal of balancing maximal analgesia with minimal adverse events. Among the therapeutic agents available, opioid analgesics are notably effective at reducing various types of pain, yet they require management of the potential adverse effects associated with their use as well as the risks for abuse, misuse, and diversion. By presenting patients with a range of chronic pain disorders, this volume illuminates these and other issues in the assessment, diagnosis, and treatment of chronic pain.

Target Audience

This program is intended for physicians who treat patients with chronic pain, including pain specialists, orthopedic surgeons, neurologists, emergency medicine physicians, rheumatologists, physical medicine and rehabilitation specialists, family practitioners, internists, general practitioners, and oncologists. There are no prerequisites for this educational program.

Learning Objectives

At the conclusion of this activity, participants should be better prepared to:

- Distinguish the clinical characteristics of different underlying etiologies of chronic pain.
- Describe the temporal characteristics and treatment challenges of baseline persistent pain and BTP.
- Explain why and how the treatment of chronic pain must be tailored to the individual patient's underlying pain disorder, functional goals, and treatment response.
- Identify types of analgesics and their clinical uses, including long-acting, short-acting, and rapid-onset opioids.
- Implement risk assessment and risk management strategies in patients receiving opioid analgesic therapy.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education.

CME Preamble

(ACCME) through the joint sponsorship of The Johns Hopkins University School of Medicine and Advanced Strategies in Medicine. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 3.0 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity. The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

Method of Participation

There are no fees for participating in and receiving credit for this activity. Participants should complete the activity and submit the self-report credit form, multiple-choice post-test answer section, and activity evaluation on pages 118 through 120 via mail to CME & Compliance, Advanced Strategies in Medicine, 545 West 45th Street, 8th Floor, New York, NY 10036. A score of at least 70% is required to successfully complete this activity. Certificates will be mailed in approximately 6 to 8 weeks after receipt of mailed submissions and verification of a passing grade. Online participation is also available via CMEZone.com (availability may be delayed from original print date). Enter the project number "CB07001" in the keyword field to directly access the activity and receive instantaneous participation. Upon participants' passing the activity, a certificate will be displayed on screen that participants can print and keep for their records. If the post-test is failed, a screen will appear alerting participants of their current score and displaying the questions that have been answered incorrectly. One retake is allowed. Credit is available through June 30, 2009.

Faculty Disclosure of Relevant Financial Relationships

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of The Johns Hopkins University School of Medicine to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

Charles E. Argoff, MD
Cephalon, Inc, GlaxoSmithKline (grant/research support); Allergan, Inc, Cephalon, Inc, Eli Lilly and Company, Endo Pharmaceuticals, Inc, GlaxoSmithKline,

Merck & Co, Inc, Pfizer Inc, PriCara (consultant); Eli Lilly and Company, Endo Pharmaceuticals, Inc, Merck & Co Inc, Pfizer Inc, PriCara (honoraria); Eli Lilly and Company, Endo Pharmaceuticals, Inc, Merck & Co, Inc, Pfizer Inc, PriCara (speakers' bureaus)

Michael J. Brennan, MD
Alpharma, Inc, Cephalon, Inc, Eli Lilly and Company, Endo Pharmaceuticals, Inc, King Pharmaceuticals, Inc, Pfizer Inc, Purdue Pharma, LP (honoraria); Alpharma, Inc, Cephalon, Inc, Eli Lilly and Company, Endo Pharmaceuticals, Inc, King Pharmaceuticals, Inc, Pfizer Inc, Purdue Pharma, LP (speakers' bureaus)

Steven P. Cohen, MD
Dr. Cohen has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Perry G. Fine, MD
Alpharma, Inc, Cephalon, Inc, Eli Lilly and Company, Endo Pharmaceuticals, Inc, GlaxoSmithKline, Merck & Co, Inc, Wyeth Pharmaceuticals (consultant)

Contributor Disclosure of Relevant Financial Relationships

The content of this compendium is based on a roundtable workshop held on June 15, 2007. Contributing participants of the roundtable workshop reported the following:

Tamika Blackburn
Ms. Blackburn has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Feiyu Chen, MD, PhD
Dr. Chen has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Elizabeth Concepcion, MD
Dr. Concepcion has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Donald D'Angelo, MD
Dr. D'Angelo has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

CME Preamble

Martha Desmond, MSN
Ms. Desmond has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Qiang Fang, MD
Dr. Fang has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Hannah Garrick
Ms. Garrick has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Alfred Gilgore, DO
Dr. Gilgore has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Eileen Liu, MD
Dr. Liu has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Munir Merchant, MD
Dr. Merchant has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

Austin Moede, MD
Dr. Moede has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

William Morrone, DO
Dr. Morrone has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

S. Ramachandran Nair, MD
Dr. Nair has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

SVETLANA NARODITSKY, MD
Dr. Naroditsky has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

DENISE OCTAVIANI, DO
Dr. Octaviani has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

JEFFREY RANGEL, MD
Dr. Rangel has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

NICOLE SASSON, MD
Dr. Sasson has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

ROBERT TAYLOR II
Mr. Taylor has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

RAVI VELISETTI, MD
Dr. Velisetti has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

ASHA VELISETTY, MD
Dr. Velisetty has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

KEVIN ZACHAROFF, MD
Inflexxion, Inc (grant/research support); EKR Therapeutics, Inflexxion, Inc (consultant)

JOSEPH ZOLOT
Mr. Zolot has no relevant financial interest or relationships with a commercial interest whose products or services are discussed in or pertain to the content of this educational activity.

CME Preamble

Disclosure of Discussions of Off-Label and Investigational Uses of Drugs

The program will discuss unlabeled/unapproved uses of a variety of formulations of opioid and nonopioid analgesics, including fentanyl.

Disclaimer Statement

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of The Johns Hopkins University School of Medicine name or the Advanced Strategies in Medicine name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects, before administering pharmacologic therapy to patients.

Support Statement

Supported by an educational grant from Cephalon, Inc.

Note From the Editor

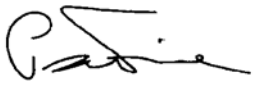
Dear Colleagues:

Pain is the most common reason why individuals seek health care. In recent years, the importance of the adequate assessment and management of pain has gained increasing recognition, evidenced by the fact that The Joint Commission has established pain as the "fifth vital sign." Chronic pain, including baseline persistent and breakthrough pain, is of particular concern to the patients who experience it and to the clinicians who are guiding their treatment. This compendium of cases has been developed to introduce the reader to key issues regarding the assessment and management of baseline persistent and breakthrough pain in a variety of clinical settings.

No single set of laboratory tests or other assessment tools is currently available to detect the presence of pain or measure its effect on the patient. Although this adds to the complexity of managing painful disorders, appropriate assessment of pain is possible, as is effective treatment. Clinicians must keep in mind the need to assess each patient individually with respect to the pain diagnosis, known treatments for that disorder, and risks of treatment for that patient. Such care is necessary when decisions are made regarding the use of opioids for moderate to severe pain that has not responded to other therapies, and in the selection of other medical, interventional, or nonmedical modalities. Pain management requires that the clinician tailor the prescribed therapy based on an ongoing assessment of the patient and an evaluation of the treatment response.

Although a book of this scope cannot include all types of pain and all situations that clinicians may encounter, it seeks to provide insights about the assessment, treatment, and ongoing monitoring of many commonly encountered chronic pain conditions. Because it provides clinical cases that can be adopted as examples or teaching tools, I am confident that this case series will be a useful addition to your library.

Sincerely,



Perry G. Fine, MD

Chapter 1: Introduction

Chronic pain is a serious and widespread problem, affecting an estimated 50 million Americans annually.[1] Unlike acute pain, which serves the important biological function of signaling potential or actual injury, chronic pain is maladaptive, offering no known survival advantage.[2] It has many causes and has traditionally been categorized based on presumed pathophysiology as nociceptive or neuropathic.[3-5] Recent studies of the diverse range of potential etiologies, however, suggest that most chronic pain states are caused by a mixture of underlying mechanisms. This has led some clinicians to propose a more mechanism-based classification of pain, which includes such pain types as nociceptive (transient pain in response to noxious stimuli), inflammatory (pain and hypersensitivity in response to tissue damage and inflammation), neuropathic (pain and hypersensitivity associated with damage to the nervous system), and functional (hypersensitivity resulting from augmented central pain processing).[6]

Regardless of pathophysiology, chronic pain usually comprises 2 notable temporal patterns—baseline persistent pain and breakthrough pain

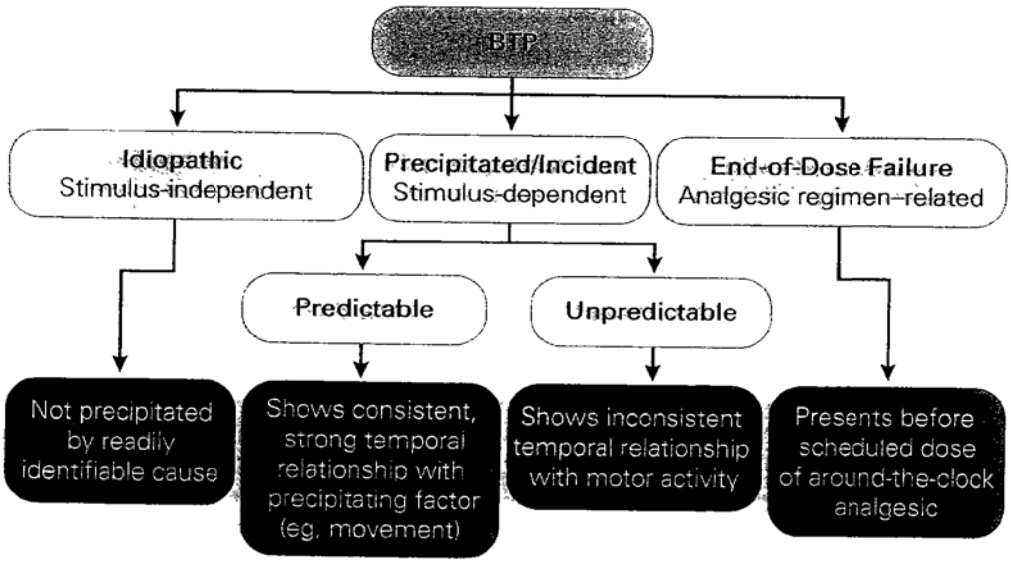


Figure 1. Characteristics and subtypes of BTP.[7,10,11]

BTP, breakthrough pain

(BTP)—which must be separately assessed and treated for optimal management to occur. Baseline persistent pain, as the name suggests, is pain that is mostly or wholly continuous. In patients with adequately controlled baseline persistent pain, BTP is a transitory pain that lasts from seconds to hours, is more severe than the background pain,[7] and negatively affects function and quality of life (QoL). BTP is highly prevalent in both cancer (50%-90%)[8] and noncancer (74%)[9] conditions. There are 3 proposed subtypes: precipitated/incident BTP, idiopathic BTP, and end-of-dose failure (Figure 1).[7,10,11] Precipitated/incident episodes are related to an identifiable stimulus that may be predictable (ie, pain with movement) or unpredictable (ie, pain with sneezing or coughing); idiopathic episodes are not precipitated by a readily identifiable cause, and end-of-dose failure occurs when the effects of a dose from an around-the-clock (ATC) analgesic regimen diminish earlier than anticipated, leading to predictable spikes in pain at the end of a dosing interval.

This compendium describes 9 patients with various presentations of baseline persistent pain and BTP, from initial assessment through diagnosis and treatment. Representing a variety of common chronic pain conditions, these patients illustrate the types of clinical scenarios encountered by pain management specialists. To increase the usefulness of the book, this introduction presents a brief overview of fundamental issues common to all the patients.

Assessment

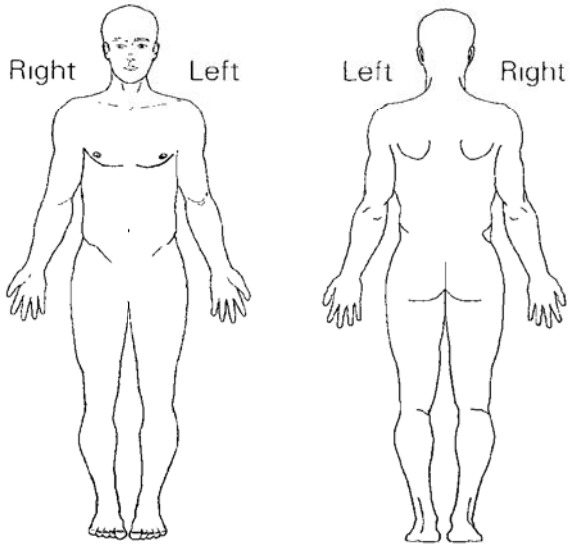
The assessment of chronic pain must be comprehensive and directed toward identifying all relevant aspects of the patient's condition, including both baseline persistent pain and BTP. A detailed history, including comorbidities and prior treatments, and thorough physical examination are requisite to diagnosis and treatment.[1] The clinician should characterize the pain by asking the patient to describe its quality, location, intensity, duration, frequency, onset, precipitants, and relieving measures. Validated pain assessment tools, appropriate to the particular patient, are recommended. These may include unidimensional scales (eg, the Numeric Rating Scale, with which patients assign their pain a value from 0 to 10) and multidimensional scales (eg, the Brief Pain Inventory [BPI[12]], an instrument that measures the intensity and location of pain, the degree of relief pain treatment has provided, and the degree to which the pain interferes with function and QoL [Figure 2, page 4]).

Figure 2. Brief Pain Inventory (Short Form).[12]

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

   1 Yes 2 No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours.

   0 1 2 3 4 5 6 7 8 9 10

   No pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its LEAST in the last 24 hours.

   0 1 2 3 4 5 6 7 8 9 10

   No pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on AVERAGE.

   0 1 2 3 4 5 6 7 8 9 10

   No pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have RIGHT NOW.

0 1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

_____

_____

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that shows how much RELIEF you have received.

0% 10 20 30 40 50 60 70 80 90 100%

No relief — Complete relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

If possible, the pathophysiology of the pain should be clarified and any underlying relevant condition identified and diagnosed as precisely as possible. The use of validated neuropathic pain rating scales, such as the Neuropathic Pain Questionnaire (NPQ) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), can help differentiate between neuropathic and non-neuropathic pain.[13,16] The NPQ, for example, consists of 12 patient-answered questions related to sensory responses such as "tingling" and patient affect. The LANSS asks whether the pain is accompanied by "pins and needles" sensations, changes in skin color, or abnormal sensitivity to touch—all often signs of neuropathic pain.

Treat the Treatable: Following Up on Diagnosis

If assessment reveals a treatable condition underlying the pain, that condition should, of course, be addressed, with the caveat that even when disease-modifying therapies are identified and initiated, the management of chronic pain is often ongoing and complex, requiring a plan tailored to the specific needs of the individual. Such a plan includes the establishment of treatment goals aimed at achieving an optimal balance between maximal analgesia and minimal adverse events. These goals focus specifically on functional outcomes related to such areas as work, recreation, social life, sexuality, mood, and sleep. They should be set at the initiation of therapy and pursued with an understanding that although complete elimination of pain may not be attainable, significant improvements in function are possible with successful treatment. This is seen, for example, in the case of Juan (Chapter 2), a patient who undergoes surgery for osteoarthritis.

The selection of nonpharmacologic and pharmacologic treatments by the clinician can be aided by published guidelines.[17-24] Often, an integrated, multimodal combination of therapies from each of these broad areas best achieves treatment goals and sustains positive outcomes. Nonpharmacologic strategies for managing chronic pain include physical, behavioral, and complementary and alternative medical approaches; pharmacologic options can be broadly categorized as nonopioids and opioids. Furthermore, pharmacologic and nonpharmacologic interventional strategies, including nerve blocks, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation, and other implantable therapies, may be useful for treating patients with chronic pain.

Nonopioid Analgesics

Nonopioid analgesics have traditionally included acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs; eg, ibuprofen and the selective cyclooxygenase-2 [COX-2] inhibitor celecoxib). In the past, when certain anticonvulsants, antidepressants, and $\alpha_2\delta$ ligands were prescribed for pain, they were referred to as adjuvant analgesics because they were initially developed for a different use and later discovered to have analgesic properties. Given that several of these agents—specifically the $\alpha_2\delta$ ligand pregabalin and the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine—now have FDA approval specifically for pain, they may be more appropriately categorized as nonopioid analgesics

Studies have shown that the selection of analgesic can also be informed by the etiopathophysiology of the pain. For example, APAP and NSAIDs are beneficial for various kinds of nociceptive inflammatory pain,[25-27] whereas medications traditionally classified as adjuvants, such as antidepressants and $\alpha_2\delta$ ligands, are particularly useful for neuropathic pain. Bisphosphonates and calcitonin may be helpful in treating metastatic bone pain and are being investigated in other disorders, such as low back pain (LBP) and complex regional pain syndrome (CRPS).[28-34]

Opioid Therapy

Opioids are effective in treating moderate to severe chronic pain. They have an established role in the treatment of cancer pain[35,36] and are increasingly being used in noncancer pain related to both neuropathic and musculoskeletal conditions.[37-39] Like all medications, opioids are associated with certain risks, such as adverse events and substance abuse, misuse, addiction, and diversion. Common adverse events include constipation, nausea, vomiting, pruritus, myoclonus, somnolence, and cognitive impairment; these usually either resolve on their own within days or can be managed with various treatment modalities—for example, motility-enhancing laxatives to prevent and treat opioid-induced bowel dysfunction or neuroleptics for nausea and vomiting.[1] More serious, but rare, complications of opioid treatment include respiratory depression and delirium, both of which may occur after inappropriately rapid titration in an opioid-naïve patient. Long-term opioid therapy has been associated with hypogonadism, and

some investigators have suggested that long-term, high-dose opioid therapy may cause frank hyperalgesia, although evidence for this latter neuroadaptive state in humans remains controversial.[38] Careful titration, patient and caregiver education, and ongoing clinical monitoring are therefore essential.[40] The following series of phases is designed to optimize prescribing of opioid medications.[40,41]

Decision Phase

During the decision phase, the clinician evaluates the patient and infers the pain pathophysiology to formulate a therapeutic plan, considering the benefits and risks of opioids, along with those of other appropriate therapies. For a patient with moderate to severe chronic pain who has not previously been treated with opioids, treatment with a nonopioid regimen generally should be deemed suboptimal before long-term opioid therapy is prescribed.

Risk-Assessment Phase

If opioids are regarded as appropriate for the pain state, the clinician performs an assessment for potential risk factors associated with opioid misuse, such as mood disorders, heavy smoking, and personal or family history of substance abuse. This is part of a Universal Precautions approach, in which certain safeguards are applied to all patients on the assumption that it is impossible to always initially identify those who are most at risk for misusing or diverting their medications (Table 1).[42] This is, in principle, similar to the approach taken in the management of infectious diseases. Because it is impossible to always know the exact status of a patient (eg, HIV status), gloving and other precautions are incorporated as standard procedures.

Validated risk screening tools are available to help the clinician further assess individual patients, including the Opioid Risk Tool (ORT; Figure 3, page 10)[43] and the Screener and Opioid Assessment for Patients with Pain-Revised Version (SOAPP-R).[44] Urine drug testing (UDT) also may be advisable before opioid prescribing to establish baseline values against which future test results can be compared and to confirm patient attestations concerning other substance use. Finally, a written treatment agreement may be used to educate patients and caregivers and to establish goals, rules, and expected outcomes of opioid treatment while the patient is under the

Table 1. Universal Precautions In Pain Medicine[42]

1. Make a diagnosis with an appropriate differential.
2. Perform a psychological assessment, including risk for addictive disorders.
3. Obtain informed consent.
4. Obtain a treatment agreement.
5. Perform a pre- and post-intervention assessment of pain score and level of function.
6. Initiate an appropriate trial of opioid therapy with or without adjunctive medication.
7. Reassess pain score and level of function.
8. Regularly assess the patient for the 4 A's of pain medicine:
   - Analgesia
   - Activities of daily living
   - Adverse events
   - Aberrant drug-taking behavior
9. Periodically review the pain diagnosis and comorbid conditions, including addictive disorders.
10. Provide documentation.

clinician's care (Figure 4, page 12).

Risk assessment provides the clinician with information to stratify patients and structure opioid therapy accordingly. For example, Gordon (Chapter 5), a patient with CRPS who is regarded as low-risk at his initial assessment, is placed on opioid therapy with a follow-up appointment at 4 weeks. By contrast, Wendy (Chapter 9), a patient with irritable bowel syndrome (IBS) who visits more than one physician in an effort to obtain additional morphine (known as doctor shopping), is required to discontinue that behavior and adhere to a more structured treatment regimen—she must see her physician at 1-week intervals, agree to pill counts and periodic UDT, and consult with an addiction specialist. Although the need for greater structure emerges only during the course of Wendy's treatment, such safeguards may be needed at the outset if the initial assessment suggests that a patient is high-risk.

Figure 3. Opioid Risk Tool[43]

Mark each box that applies	Female	Male
1. Family history of substance abuse		
• Alcohol	❑ 1	❑ 3
• Illegal drugs	❑ 2	❑ 3
• Prescribing drugs	❑ 4	❑ 4
2. Personal history of substance abuse		
• Alcohol	❑ 3	❑ 3
• Illegal drugs	❑ 4	❑ 4
• Prescribing drugs	❑ 5	❑ 5
3. Age (mark box if between 16-45 years)	❑ 1	❑ 1
4. History of preadolescent sexual abuse	❑ 3	❑ 0
5. Psychological disease		
• ADD, OCD, bipolar, schizophrenia	❑ 2	❑ 2
• Depression	❑ 1	❑ 1

Scoring (total): 0-3, low risk; 4-7, moderate risk, ≥8, high risk.

ADD, attention-deficit disorder, **OCD,** obsessive-compulsive disorder.

Dose-Adjustment Phase

In the dose-adjustment phase, an opioid medication is titrated over a period of days to weeks, with the goal of attaining a stable, effective dose. Opioid medications are broadly categorized according to their pharmacokinetic and pharmacodynamic properties as long-acting opioids (LAOs), short-acting opioids (SAOs), or rapid-onset opioids (ROOs; Figure 5, page 14). SAOs have been shown to be effective in controlling both cancer and noncancer chronic pain, and they may be especially useful in treating intermittent pain.[45-47] They are recommended for initial titration and often replaced by LAOs once the desired analgesia is achieved, although this prescribing practice is not always followed.

LAOs have a strong record of efficacy and safety in both chronic cancer and noncancer pain.[48-50] These agents typically are recommended over SAOs for treating the unremitting baseline persistent component of chronic pain. Comprehensive evidence supporting this practice is lacking: a systematic review in adults with chronic noncancer pain found no consistent differences in safety and efficacy

between LAOs and SAOs [38] Yet clinical experience suggests that the use of LAOs for chronic pain is warranted, both for patient convenience (perhaps improving adherence) and because long-acting formulations may maintain the drug concentration at an effective level over a longer period of time.[51]

Stable Phase

During the stable phase, the goal is to maintain the opioid dose to the extent possible while regularly monitoring the "4 A's". Analgesia, Activities of daily living (ADLs), Adverse events, and Aberrant drug-taking behaviors.[52,53] Aberrant drug-taking behaviors may range from those proposed to be less predictive of abuse or misuse, such as requesting specific drugs or hoarding medications, to those more predictive of abuse or misuse, such as selling prescription drugs or forging prescriptions.[54] Careful documentation of the 4 A's is an important aspect of risk management, demonstrating the physician's appropriate oversight of prescribed controlled substances.

It is important to note that not every instance of aberrant drug-taking behavior is a sign of addiction.[55] Addiction is a neurobiologic disease characterized by impaired control over drug use, craving, compulsive use, and continued use despite harm.[55,56] When behaviors suggest excessive drug seeking or addiction, the differential diagnosis of such behaviors should be considered in the clinical context of a good doctor–patient relationship. For example, a patient may run out of a prescription and request an early refill because he or she is abusing the drug or because inadequate analgesia is prompting self-escalation in dosing. Both are aberrant behaviors, but the latter suggest pseudoaddiction,[55] which indicates inadequate pain control. Other behaviors, such as altering the route of delivery of a drug by chewing or snorting an oral formulation, are highly indicative of abuse and addiction.[57]

Clinicians should be aware that patients may be involved in diversion, the intentional redirecting of a medication from legitimate to illegal channels, which is a criminal act that certainly also is grounds for the termination of opioid treatment.[58,59] Prescribing clinicians have a responsibility to do their best to recognize and minimize this type of illicit activity—although not at the expense of limiting access to analgesics for patients with legitimate medical need who are not displaying

Figure 4. Sample opioid treatment agreement.

Patient Agreement: Long-term Controlled Substances Therapy for Chronic Pain

The purpose of this agreement is to protect your access to controlled substances and to protect our ability to prescribe for you.

The long-term use of such substances as opioids (narcotic analgesics), benzodiazepine tranquilizers, and barbiturate sedatives is controversial because of uncertainty regarding the extent to which they provide long-term benefit. There is also the risk for an addictive disorder developing or of relapse occurring in a person with a prior addiction. The extent of this risk is not certain.

Because these drugs have a potential for abuse or diversion, strict accountability is necessary when use is prolonged. For this reason, the following policies are agreed to by you, the patient, as consideration for, and a condition of, the willingness of the physician whose signature appears below to consider the initial and/or continued prescription of controlled substances to treat your chronic pain.

1. All controlled substances must come from the physician whose signature appears below or, during his or her absence, the covering physician, unless specific authorization is obtained for an exception. (Multiple sources can lead to untoward drug interactions or poor coordination of treatment.)
2. All controlled substances must be obtained at the same pharmacy, where possible. Should the need arise to change pharmacies, our office must be informed. The pharmacy that you have selected is:

   _____

   Phone:_____
3. You are expected to inform our office of any new medications or medical conditions, and of any adverse effects you experience from any of the medications that you take.
4. The prescribing physician has permission to discuss all diagnostic and treatment details with dispensing pharmacists or other professionals who provide your health care for purposes of maintaining accountability.
5. You may not share, sell, or otherwise permit others to have access to these medications.
6. These drugs should not be stopped abruptly, as an abstinence syndrome will likely develop
7. Unannounced urine or serum toxicology screens may be requested, and your cooperation is required. Presence of unauthorized substances may prompt referral for assessment for addictive disorder
8. Prescriptions and bottles of these medications may be sought by other individuals with chemical dependency and should be closely safeguarded. It is expected that you will take the highest possible degree of care

with your medication and prescription. They should not be left where others might see or otherwise have access to them

9 Original containers of medications should be brought in to each office visit

10. Because the drugs may be hazardous or lethal to a person who is not tolerant to their effects, especially a child, you must keep them out of reach of such people

11. Medications may not be replaced if they are lost, get wet, are destroyed, left on an airplane, etc. If your medication has been stolen and you complete a police report regarding the theft, an exception may be made

12. Early refills will generally not be given

13 Prescriptions may be issued early if the physician or patient will be out of town when a refill is due. These prescriptions will contain instructions to the pharmacist that they not be filled prior to the appropriate date.

14. If the responsible legal authorities have questions concerning your treatment, as might occur, for example, if you were obtaining medications at several pharmacies, all confidentiality is waived and these authorities may be given full access to our records of controlled substances administration

15. It is understood that failure to adhere to these policies may result in cessation of therapy with controlled substance prescribing by this physician or referral for further specialty assessment.

16. Renewals are contingent on keeping scheduled appointments. Please do not phone for prescriptions after hours or on weekends.

17. It should be understood that any medical treatment is initially a trial, and that continued prescription is contingent on evidence of benefit.

18. The risks and potential benefits of these therapies are explained elsewhere [and you acknowledge that you have received such explanation].

19. You affirm that you have full right and power to sign and be bound by this agreement, and that you have read, understand, and accept all of its terms.

_____

Physician Signature

_____

Patient Signature

_____

Date

_____

Patient Name (Please print)

Source American Academy of Pain Medicine

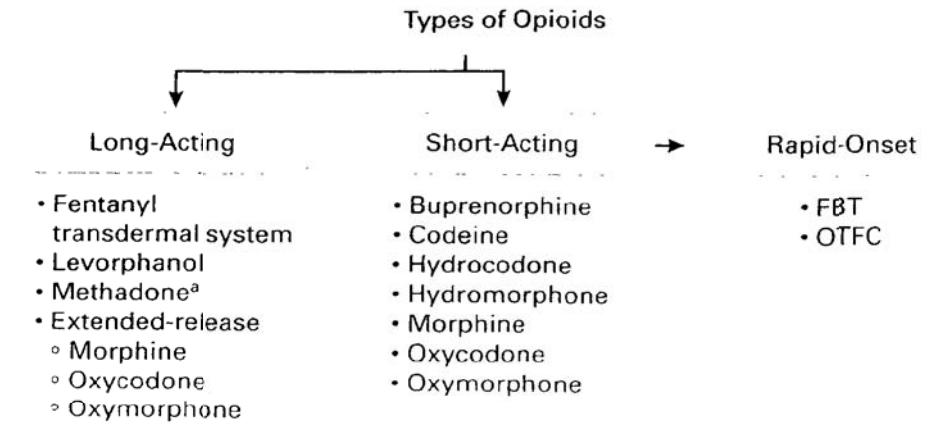


Figure 5. Opioid classification.

[a] Analgesic effects are often shorter-lived than effective metabolites
FBT, fentanyl buccal tablet, **OTFC**, oral transmucosal fentanyl citrate
Compounds in development (Phase III or later): hydromorphone CR, oxycodone CR, oxycodone CR-naltrexone combination, morphine CR-naltrexone combination (long-acting), oxycodone IR-niacin combination (short-acting), sublingual fentanyl tablet, sublingual fentanyl spray, intranasal morphine (rapid-onset)

such behavior. This dual obligation, termed the principle of balance, has been endorsed by the Federation of State Medical Boards of the United States.[60]

In response to aberrant behavior (such as Wendy's), the clinician may resort to a "brief intervention"[61] in which the patient is confronted with the problem and allowed to explain and change his or her behavior. The result may be a restructuring of therapy. In some cases, a therapeutic maneuver can aid in the differential diagnosis: raising the dose is likely to resolve a case of pseudoaddiction, but not genuine addiction.

Consultation and comanagement with addiction specialists may be considered for problematic patients, especially when a clinician does not have expertise in this area.[42,60] Such an approach was explored in a recent study that tracked the outcomes of the Opioid Renewal Clinic, a structured program designed to assist primary care physicians (PCPs) in using opioids to treat chronic noncancer pain patients who had previously misused their medication.[62] Supported by a nurse practitioner, clinical pharmacist, and multidisciplinary team of consultants, PCPs in the program required patients to sign an opioid treatment agreement as well as undergo frequent UDT. Of the patients referred

for aberrant drug-taking behaviors (n=171), 45% adhered to the opioid treatment agreement, 38% self-discharged when the structured program was offered, 13% were referred for addiction treatment, and 4% whose UDT results were consistently negative for the prescribed agents had their opioids successfully tapered according the methods established by the investigators. The results suggest the potential utility of a multidisciplinary approach to the management of opioid therapy by PCPs—even in problematic patients with chronic noncancer pain

After a stable dose has been attained, adjustment of that dose or augmentation with another agent may be required because of disease progression, the development of tolerance, or other factors. In many cases, the rational use of multidrug therapy—combining several medications to affect multiple pain mechanisms in the peripheral and central nervous systems—is warranted (Figure 6, page 16) [1,24] For example, nonopioids and opioids each target various points along the pain-signaling pathways, including 4 distinct processes involved in the experience of pain: transduction, transmission, modulation, and perception.[63] Thus, combinations of analgesics may lead to additive or synergistic analgesia.[64,65] Moreover, multidrug therapy with 2 or more drugs from different classes may result in adequate pain relief with lower doses of each agent than would be required if they were administered as monotherapy; this approach can reduce the incidence and severity of adverse events. In a recent study, for example, the combination of gabapentin and morphine provided more effective analgesia at lower doses for patients with chronic neuropathic pain than treatment with either drug alone.[65]

Once a patient's baseline persistent pain is controlled, the clinician can independently assess and treat BTP. Management of BTP is important, as studies of patients with chronic pain have shown that the presence of BTP is associated with significantly impaired QoL, higher levels of depression and anxiety, and greater health care costs.[6,66] The approach to treating BTP will depend on the subtype. End-of-dose failure may call for upward titration of the LAO and/or shortening the dosing interval, whereas predictable incident BTP may be pretreated with an SAO or ROO. Idiopathic BTP, which occurs unpredictably and therefore precludes pretreatment, requires a treatment modality with a similarly rapid onset.

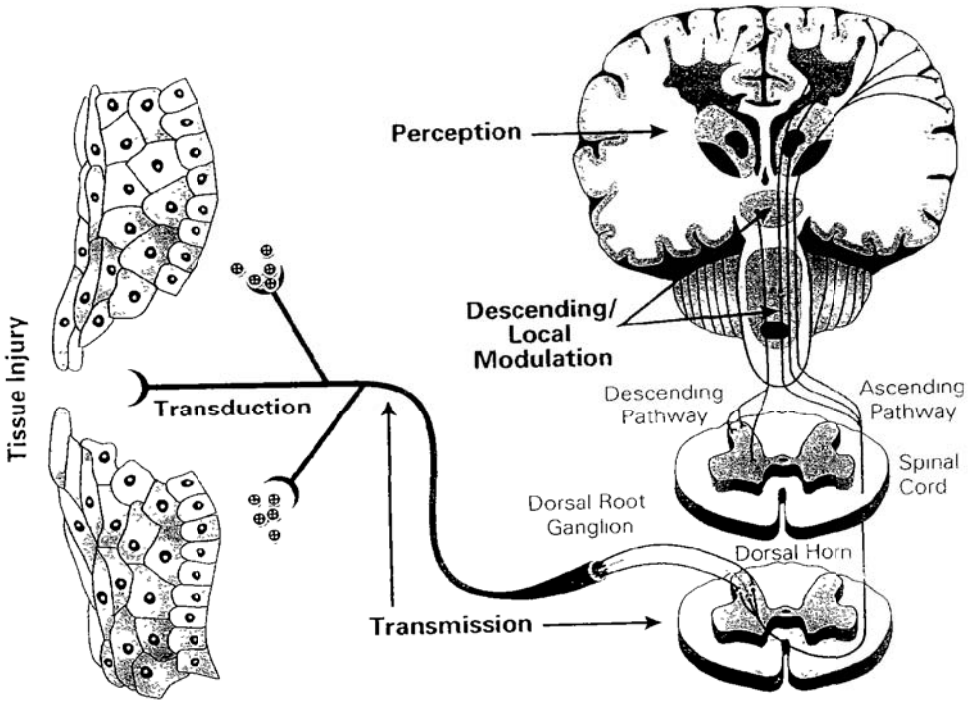


Figure 6. Targets for rational multidrug therapy.[1,24]

The ROOs—oral transmucosal fentanyl citrate (OTFC) and the more recently developed fentanyl buccal tablet (FBT)—are particularly well suited as "rescue doses" to treat unpredictable incident BTP and idiopathic BTP because their temporal characteristics most closely approximate those of the typical BTP episode. Traditional SAOs require 30 to 60 minutes to take effect, whereas a paroxysmal, idiopathic BTP episode may reach maximal severity within 3 minutes.[67,68] The onset of meaningful pain relief is within 15 minutes for OTFC and within 10 minutes for FBT.[69-75] The fentanyl in OTFC and FBT is highly lipophilic, readily crossing the buccal membranes and the blood–brain barrier. The FDA has approved both of these formulations for cancer-related BTP in opioid-tolerant patients. Patients considered opioid-tolerant are those who are taking ATC medicine consisting of a minimum of 60 mg of oral morphine daily, 25 mcg of transdermal fentanyl per hour, 30 mg of oxycodone daily, 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid daily for 1 week or longer.[76] In the OTFC formulation, fentanyl is embedded in a matrix that dissolves in the mouth when the patient actively "rubs" it against the oral mucosa.[71] FBT does not require this; rather, the tablet is placed in

the buccal fold, where an effervescent reaction enhances the extent and speed of absorption of fentanyl.[72] Because of the powerful effects of ROOs, physicians are advised to consult the important safety information in the package inserts for these products.

Other opioids, nonopioids, and interventional modalities can play a useful role in an individual patient's treatment regimen,[77,78] and various novel investigational treatments are in late-stage development

If the outcome of therapy is not acceptable, the physician should reconsider the treatment plan and modify it accordingly. In the event that response is lacking or adverse events outweigh therapeutic benefits, the clinician can consider substitution of a different opioid, referred to as opioid rotation.[79] Individuals vary in their sensitivities to the analgesic and adverse effects of particular opioids, in part because of genetic polymorphisms in opioid receptors. This variation precludes the a priori selection of the "best" opioid for each patient. Thus, clinicians need to be familiar with a range of available opioid analgesics, including their pharmacokinetic and pharmacodynamic profiles.

In some instances, opioid treatment trials fail. Patients may be unresponsive to this class of medications, adverse events may occur without adequate analgesia despite opioid rotation, and aberrant drug-taking behaviors may make the continuation of therapy with controlled substances inadvisable.[79] In addition, the underlying disease may progress in such a way that pharmacologic treatment is no longer the best option. If opioids prove unsuitable, the clinician can consider other multimodal approaches combining nonopioid drugs, interventional strategies, rehabilitation, and cognitive-behavioral therapy (CBT).[1]

Conclusion

Chronic pain is a serious condition that must be assessed and treated effectively with nonpharmacologic and pharmacologic therapies. Both components of chronic pain—baseline persistent pain and BTP—need to be adequately addressed. Opioid therapy can be a valuable component of an overall treatment plan for a patient with chronic pain when it is prescribed following a risk assessment and administered with appropriately structured monitoring, and when it demonstrates efficacy with acceptable adverse effects.

References

1 National Pharmaceutical Council (NPC) and Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Pain. current understanding of assessment, management, and treatments. December 2001 www.npcnow org/resources/PDFs/painmonograph pdf Accessed November 15, 2007

2 Woolf CJ. Somatic pain—pathogenesis and prevention *Br J Anaesth* 1995,75(2):169-176.

3 Caraceni A, Portenoy RK An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain International Association for the Study of Pain *Pain* 1999,82(3) 263-274

4 Jensen T. Mechanisms of neuropthic pain In. Campbell JN, ed *Pain 1996—An Updated Review* Seattle, WA IASP Press; 1996 77-86.

5 Merskey M, Bogduk N, eds *Classification of Chronic Pain* Seattle, WA IASP Press; 1994:21.

6 Woolf CJ, American College of Physicians, American Physiological Society. Pain. moving from symptom control toward mechanism-specific pharmacologic management. *Ann Inter Med.* 2004,140(6) 441-451.

7 Bennett D, Burton AW, Fishman S, et al Consensus panel recommendations for the assessment and management of breakthrough pain. Part 1 Assessment *Pharmacol Ther.* 2005,30(5) 296-301 Part 2 Management. *Pharmacol Ther.* 2005,30(6):354-361

8 Portenoy RK, Payne D, Jacobsen P. Breakthrough pain. characteristics and impact in patients with cancer pain *Pain.* 1999;81(1-2):129-134.

9. Portenoy RK, Bennett DS, Rauck R, et al Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. *J Pain.* 2006;7(8):583-591.

10 Driver LC Case studies in breakthrough pain. *Pain Med.* 2007;8(S1): S14-S18

11. Svendsen KB, Andersen S, Arnason S, et al Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms *Eur J Pain.* 2005;9(2):195-206.

12. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994,23(2):129-138.

13. Bennett M. The LANSS Pain Scale: the Leeds Assessment of Neuropathic Symptoms and Signs *Pain.* 2001,92(1-2).147-157.

14. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *J Pain.* 2005;6(3).149-158

15 Backonja MM, Krause SJ. Neuropathic Pain Questionnaire—Short Form *Clin J Pain* 2003;19(5):315-316.

16. Krause SJ, Backonja MM. Development of a neuropathic pain questionnaire. *Clin J Pain.* 2003;19(5).306-314

17 Fine PG. The evolving and important role of anesthesiology in palliative care. *Anesth Analg*. 2005;100(1):183-188.

18. Argoff CE, Backonja MM, Belgrade MJ, et al. Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain. *Mayo Clin Proc*. 2006;81(4 suppl):S12-S25.

19. Dworkin RH, O'Connor AB, Backonja M. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132(3):237-251.

20 Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007;146(2):116-127.

21 Armon C, Argoff CE, Samuels J, Backonja MM; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: use of epidural steroid injections to treat radicular lumbosacral pain: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2007;68(10):723-729.

22. Trescot AM, Chopra P, Abdi S, Datta S, Schultz DM. Systematic review of effectiveness and complications of adhesiolysis in the management of chronic spinal pain: an update. *Pain Physician*. 2007;10(1):129-146.

23. Boswell MV, Trescot AM, Datta S, et al. Interventional techniques: evidence-based practice guidelines in the management of chronic spinal pain. *Pain Physician*. 2007;10(1):7-111.

24. Wallace JM. Update on pharmacotherapy guidelines for treatment of neuropathic pain. *Curr Pain Headache Rep*. 2007;11(3):208-214.

25. Geba GP, Weaver AL, Polis AB, et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial [published correction appears in *JAMA* 2002;287(8):989]. *JAMA*. 2002;287(1):64-71.

26. Pincus T, Koch G, Lei H, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis*. 2004;63(8):931-939.

27. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. *Ann Rheum Dis*. 2004;63(8):901-907.

28 Semenchuk MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. *Neurology*. 2001;57(9):1583-1588.

29 Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology*. 2003;60(8):1274-1283.

30 Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. *Oncologist*. 2004;9(5):571-591.

31. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280(21):1837-1842.

32 Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy. a double-blind, placebo-controlled study [published correction appears in *Pain*. 2005,113(1-2) 248] *Pain* 2004,110(3) 697-706.

33. Sindrup SH, Gram LF, Brøsen K, Eshøj O, Mogensen EF The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms *Pain*. 1990,42(2).135-144.

34 Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. *Basic Clin Pharmacol Toxicol* 2005;96(6).399-409

35 Dews TE, Mekhail N Safe use of opioids in chronic noncancer pain. *Clev Clin J Med* 2004;71(11) 897-904

36 Bruera E, Kim HN. Cancer pain. *JAMA* 2003,290(18):2476-2479

37 Trescot AM, Boswell MV, Atluri SL, et al. Opioid guidelines in the management of chronic non-cancer pain *Pain Physician* 2006,9(1).1-40

38. Chou R, Clark E, Helfand M Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review *J Pain Symptom Manage*. 2003;26(5).1026-1048.

39 Kalso E, Edwards JE, Moore RA, McQuay HJ Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380.

40. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003, 349(20):1943-1953.

41. Fine PG, Portenoy RK *A Clinical Guide to Opioid Analgesia*. 2nd ed. New York, NY Vendome Press; 2008

42. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine. a rational approach to the treatment of chronic pain. *Pain Med*. 2005;6(2): 107-112.

43 Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. *Pain Med*. 2005;6(6): 432-442.

44 Butler SF, Fernandez KC, Benoit C, Budman SH, Jamison RN. Validation of the Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). *J Pain*. 2008;9(4):360-372.

45. Stambaugh JE, Reder RF, Stambaugh MD, Stambaugh H, Davis M Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate-release oral oxycodone in cancer pain patients. *J Clin Pharmacol*. 2001;41(5):500-506

46. Kamboj SK, Tookman A, Jones L, Curran HV. The effects of immediate-release morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care *Pain*. 2005,117(3).388-395.

47 Marcus DA. Treatment of nonmalignant chronic pain. *Am Fam Physician*. 2000;61(5):1331-1338,1345-1346.

48 Rauck RL, Bookbinder SA, Bunker TR, et al A randomized, open-label study of once-a-day AVINZA (morphine sulfate extended-release capsules) versus twice-a-day OxyContin (oxycodone hydrochloride controlled-release tablets) for chronic low back pain: the extension phase of the ACTION trial *J Opioid Manag.* 2006,2(6) 325-328, 331-323

49 Rauck RL, Bookbinder SA, Bunker TR, et al. The ACTION study: a randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin) for the treatment of chronic, moderate to severe low back pain. *J Opioid Manag* 2006;2(3).155-166.

50 Nicholson B, Ross E, Weil A, Sasaki J, Sacks G Treatment of chronic moderate-to-severe non-malignant pain with polymer-coated extended-release morphine sulfate capsules *Curr Med Res Opin* 2006,22(3): 539-550.

51 Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E Opioids for chronic non-cancer pain: a meta-analysis of effectiveness and side effects *CMAJ* 2006,174(11) 1589-1594

52 Passik SD, Weinreb HJ Managing chronic nonmalignant pain. overcoming obstacles to the use of opioids *Adv Ther.* 2000;17(2).70-83

53 Passik SD, Kirsh KL Managing pain in patients with aberrant drug-taking behaviors *J Support Oncol* 2005;3(1).83-86

54 Passik SD, Kirsh KL Chronic pain management and substance abuse—assessing and optimizing outcomes *Elder Care.* September 2002;1-3

55. Weaver M, Schnoll S Abuse liability in opioid therapy for pain treatment in patients with an addiction history. *Clin J Pain.* 2002;18(4 suppl):S61-S69

56. Passik SD, Kirsh KL, Donaghy KB, Portenoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clin J Pain* 2006,22(2) 173-181.

57. Katz NP, Adams EH, Chilcoat H, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain.* 2007;23(8) 648-660

58 The National Center on Addiction and Substance Abuse at Columbia University (CASA). *Under the Counter: the Diversion and Abuse of Controlled Prescription Drugs in the U.S* New York, NY: CASA; 2005.

59. Gilson AM, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control. 1997-2002. *J Pain Symptom Manage* 2004;28(2):176–188.

60. Federation of State Medical Boards of the United States, Inc Model policy for the use of controlled substances for the treatment of pain. May 2004. http://www.fsmb.org/pdf/2004_grpol_Controlled_Substances pdf Accessed January 31, 2008.

61. Passik SD, Kirsh KL Opioid therapy in patients with a history of substance abuse. *CNS Drugs.* 2004;18(1):13-25.

62 Wiedemer NL, Harden PS, Arndt IO, Gallagher RM The Opioid Renewal Clinic a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse *Pain Med* 2007;8(7) 573-584.

63 Woolf CJ Pain moving from symptom control toward mechanism-specific pharmacologic management *Ann Intern Med* 2004,140(6) 441-451.

64 Keskinbora K, Pekel AF, Aydinli I Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain a randomized open trial *J Pain Symptom Manage* 2007,34(2)·183-189.

65. Gilron I, Bailey JM, Tu D, et al Morphine, gabapentin, or their combination for neuropathic pain *N Engl J Med.* 2005,352(13) 1324-1334.

66 Fortner BV, Okon TA, Portenoy RK, et al A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain *J Pain.* 2002,3·38-44

67 Portenoy RK, Hagen NA. Breakthrough pain definition, prevalence and characteristics. *Pain* 1990;41(3).273-281.

68. Tennant F, Herman L, Reinking JC, Snyder N The use of oral transmucosal fentanyl citrate for breakthrough pain in severe, non-malignant chronic pain. *J Pain Symptom Manage.* 2002,12(4):130-135.

69. Darwish M, Tempero K, Kirby M, Thompson J. Relative bioavailability of the fentanyl effervescent buccal tablet (FEBT) 1080 µg versus oral transmucosal fentanyl citrate 1600 µg and dose proportionality of FEBT 270 to 1300 µg: a single-dose, randomized, open-label, three-period study in healthy adult volunteers. *Clin Ther* 2006,28(5):715-724

70. Portenoy RK, Payne R, Coluzzi P, et al Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients. a controlled dose titration study. *Pain.* 1999;79(2-3)·303-312

71 Fine PG, Marcus M, De Boer AJ, Van der Oord B. An open label study of oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough cancer pain. *Pain.* 1991;45(2):149-153

72 Simpson DM, Messina J, Xie F, Hale M Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther.* 2007;29(4):588-601.

73. Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain *J Support Oncol.* 2007;5(7):327-334.

74 Fine PG, Messina J, Peppin JF. Management of breakthrough pain in opioid-tolerant patients with chronic low back pain or neuropathic pain: combined analysis of two randomized, double-blind studies of fentanyl buccal tablet *J Pain* 2007;8(4 suppl 1).S43.

75. Fentora (fentanyl buccal tablet) [prescribing information]. Frazer, PA Cephalon, Inc, 2007.

76. Fine PG. *The Diagnosis and Treatment of Breakthrough Pain.* New York, NY: Oxford University Press; 2008.

77 Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. *Can J Anaesth* 2001;48(10):1000-1010.

78. Yaksh TL. Future advances in pain pharmacology: what does the present say about the future? *Proc West Pharmacol Soc* 2002;45:211-218.

79. Indelicato RA, Portenoy RK. Opioid rotation in the management of refractory cancer pain. *J Clin Oncol*. 2002;20(1):348-352.

Chapter 2: Juan

A Patient With Osteoarthritis

Case

Juan, a 66-year-old retired man, presents to his PCP with intense pain in his right knee. This pain has been present for approximately 1.5 years, but in the 6 months before his visit to the doctor, it has begun to limit his activity. A widower, he has remained socially active in large part by dancing tango and salsa, but the pain interferes with his ability to engage in these activities. Once, while he was dancing, his leg buckled and he fell. Frightened and embarrassed, he stopped dancing and began to spend more time alone at home. He reports feeling anxious about aging and his waning activity level

Current Medications

Juan takes atenolol 50 mg daily, APAP 1,000 mg 3 times daily, and ibuprofen 200 mg 4 times daily. This regimen helps somewhat but does not allow him to function normally.

Medical History

Juan has a history of hypertension controlled by atenolol. He is overweight and has no history of diabetes mellitus (DM), cancer, or other illnesses.

Family History

Juan's family history is notable for his father's death from a heart attack at age 41.

Social History

Juan lives alone. He has a number of friends whom he sees often, although his knee-related incapacity has recently limited his ability to visit them. His 2 children are supportive but live too far away to help take care of him. In any event, he resists the idea of needing support or a caretaker.

Juan worked as a bicycle courier for 5 years after immigrating to the United States from Argentina at age 20. After that, he took a job as a

clerk and eventually became an office manager. He held that position until his retirement 2 years ago. He previously enjoyed recreational bicycle tours with his wife. Juan smoked socially when he was young, but he has not done so in 20 years. He drinks approximately 5 alcoholic beverages a week.

Examination and Diagnosis

Juan reports chronic pain and stiffness in his knees for 15 minutes after he awakens as well as flares of pain when dancing and walking long distances. He rates the chronic persistent pain at 4-6/10 and the episodic pain at 8-9/10. Additionally, he reports crepitus and weakness, particularly when ascending or descending stairs.

Juan's blood pressure (BP) is 130/80 mm Hg, his heart rate (HR) is 68 beats/min, and his body mass index (BMI) is 28.8 kg/m^2. The physician conducts additional tests in an attempt to determine the cause of Juan's pain. Physical examination reveals mild swelling in the right knee, with a mild varus deformity. His gait is antalgic. There is pain on palpation over the lateral and medial tibial–femoral joint, and crepitus is both heard and felt There is no erythema and the joint is not warm, nor is there apparent effusion. No evidence of ligamentous laxity is observed. Range of motion is full on the left but lacking 10 degrees of extension on the right. X-ray imaging of his right knee reveals moderate to severe degenerative changes with severe joint space narrowing (Figure 1, page 26). Although the physician suspects degenerative osteoarthritis (OA), he wishes to rule out inflammatory disease and orders laboratory tests that include examinations of the serum erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF). The physician also aspirates synovial fluid from the left knee for analysis. Results of all laboratory tests are normal. On the basis of these results, Juan is given a diagnosis of OA.

Treatment and Management

The physician discusses the full range of potential therapies, including intra-articular injection, rehabilitation, and joint replacement, and recommends a trial of a combination of pharmacologic and nonpharmacologic strategies to help Juan. He advises Juan to continue his current medication regimen and begin a low-impact physical exercise program to reduce his pain, help him lose weight, and strengthen his muscles.

Figure 1. X-rays of Juan's right knee showing degenerative osteoarthritic changes.

Juan elects to begin swimming and water running. At a follow-up visit 3 weeks later, Juan reports that the combination of APAP and ibuprofen plus exercise has reduced his chronic pain to 2-4/10 but has had little effect on the pain flares. The physician advises Juan to discontinue the ibuprofen. Trials of naproxen at a dosage of 500 mg twice daily and then etodolac 400 mg 3 times daily fail to provide adequate relief.

Juan is then treated with tramadol, which does not provide sufficient relief and causes dizziness and nausea. At this point Juan is offered a trial of hyaluronic acid for viscosupplementation. A series of 5 injections has minimal benefit. Because of his concern over postsurgical pain, Juan is reluctant to pursue surgical evaluation for knee replacement surgery unless absolutely necessary.

The physician then considers prescribing an opioid to achieve better control of the baseline persistent pain as well as the activity-related BTP. Juan scores 0 on the ORT and signs an opioid treatment agreement that explains the risks and benefits of opioids and affirms his willingness to adhere to the prescribed treatment regimen, including keeping scheduled follow-up appointments and undergoing UDT. The physician prescribes 10 mg of oxycodone controlled-release (CR) every 12 hours. Two weeks later, Juan reports that this regimen is only partially effective for his chronic pain, fails to provide satisfactory relief of his BTP, and causes constipation. The physician recommends the combination of a natural senna product for improved bowel

motility, to be used nightly, and psyllium, a bulk-forming laxative, at an initial dosage of 1 tbsp 3 times daily, and instructs Juan to take each dose with a large glass of water. This relieves his constipation, but the oxycodone CR remains an unsatisfactory therapy even when titrated up to 20 mg every 12 hours.

Given these results, the physician recommends further evaluation for joint replacement surgery. Juan agrees to undergo the procedure, and after recovery, he is able to return to his previous routines and resume his social life. He reports reduced pain, increased activity, and greater confidence in his body and his ability to live independently. However, he still has significant flares of pain when dancing. The physician prescribes short-acting oxycodone 5 mg/APAP 325 mg up to 4 times daily as needed and instructs Juan to take the medication 30 minutes before his dance class. This brings Juan's pain under control.

Discussion

OA is the most common joint disorder in the world.[1] It occurs frequently in older patients and after joint trauma. In Western countries, radiographic evidence of OA is present in the majority of people by the age of 65 and in about 80% of those who are 75 or older. The consequences of OA-related pain, especially flares, include diminished QoL and loss of function. OA can take a significant toll not only on the musculoskeletal system but also on the body as a whole. Therefore, the goals of treatment should be to relieve pain and improve muscle function, strength, and conditioning while preserving the patient's independence, mobility, and QoL.

Characterized by the degeneration of articular cartilage and adjacent tissues, such as bone, synovial joint capsule, muscle, and ligament, OA manifests as joint pain, stiffness, and instability. Symptoms of OA in the knee, including pain and reduced function, may be exacerbated by trauma, obesity, and psychological factors. Signs include muscle atrophy due to limited movement, joint deformity, joint buckling, altered gait, and crepitus. Pain resulting from OA can be related to various sources, including inflammation, increased intramedullary tension and/or microfractures in subchondral bone, bony spurs (osteophytes), muscle spasm/contracture, and bone marrow lesions. Radiculopathy may also occur when osteophytes, particularly in the spine, exert pressure on surrounding nerves.

OA is diagnosed through history, physical examination, radiography, and, when necessary, magnetic resonance imaging (MRI) and arthroscopic examination. If OA is present, as in Juan's case, results of laboratory tests will typically be normal, showing an ESR of less than 40 mm/h (adjusted for age and gender) and an RF level of 40 units or lower. Radiographs of patients with OA reveal osteophytes, joint space narrowing, malalignment, and subchondral sclerosis. Bone lesions and intra-articular disease (eg, meniscus tears) can be detected by MRI.

In severe, debilitating cases, or when internal derangements of the joint are present and there is little likelihood of return to full ambulatory and weight-bearing status with conservative therapy alone, patients may require arthroscopic or knee joint replacement procedures. Otherwise, an initial approach for patients with OA should include both nonpharmacologic and pharmacologic therapy to address pain and functional and psychosocial needs. The American College of Rheumatology (ACR) recommendations for the medical management of osteoarthritis of the hip and knee emphasize nonpharmacologic approaches to treatment in conjunction with appropriate drug therapy (Table 1).[2] If surgery is indicated and performed, as in Juan's case, analgesics facilitate patient participation in functionally restorative physical therapy that can be quite painful at first.

Pharmacologic agents used to manage the pain associated with OA are APAP; NSAIDs, including the nonselective NSAIDs and COX-2 inhibitors; tramadol; pure μ-opioid receptor agonists; and topical medications. For OA of the hips and knees, the ACR criteria call for APAP as a first-line treatment.[2] APAP is an inexpensive over-the-counter (OTC) drug that is effective for mild to moderate pain. Rare cases of hepatic toxicity have been associated with excessive use of APAP, including 5 fatalities in a 3-year period at an urban hospital,[3] and APAP should be used with extra caution in patients who have liver disease or are moderate to heavy users of alcohol. APAP also may cause renal toxicity.[4] Most importantly, because many OTC medications include APAP (eg, cold remedies and pain relievers), as do several of the opioid analgesic combination products (eg, tramadol, hydrocodone, codeine, and oxycodone), physicians should be very specific about inquiring into the use of such medications and provide appropriate counseling so as to avoid inadvertent overuse of APAP (more than the maximum recommended daily dose of 4 g/d).

Table 1. Nonpharmacologic Therapy for Patients With Osteoarthritis[2]

Aerobic exercise programs
Appropriate footwear
Assistive devices for activities of daily living
Assistive devices for ambulation
Bracing
Joint protection and energy conservation
Lateral-wedge insoles (for genu varum)
Muscle-strengthening exercises
Occupational therapy
Patellar taping
Patient education
Personalized social support
Physical therapy
Range-of-motion exercises
Self-management programs
Weight loss (if overweight)

There is evidence that NSAIDs are more effective than APAP for the treatment of OA pain.[5] NSAIDs include nonselective COX-1 and COX-2 inhibitors and the only COX-2–selective inhibitor currently available in the United States, celecoxib. The World Health Organization (WHO) stepladder approach as adapted by Reig for the treatment of rheumatic pain calls for the NSAID ibuprofen as first-line treatment.[6] However, debate is ongoing as to whether the benefits of NSAIDs outweigh their cardiovascular and gastrointestinal (GI) risks. Researchers studying patients with OA of the knee reported that NSAIDs do not retain their pain reduction advantage over placebo after 2 to 4 weeks.[7] Another study suggested that the progression of OA may be accelerated by the use of NSAIDs, specifically indomethacin.[8] All NSAIDs carry a risk for upper GI complications with long-term use, although COX-2–selective agents tend to be GI tract–sparing in the short run. To mitigate ulcer risk, a proton pump inhibitor, such as omeprazole,

may be prescribed in conjunction with the NSAID. In a recent study, concomitant use of a proton pump inhibitor with an NSAID effectively reduced the risk for NSAID-induced gastropathy.[9]

Tramadol, which is widely prescribed for OA pain, is step 2 on Reig's adaptation of the WHO stepladder.[6] Tramadol inhibits the reuptake of norepinephrine and serotonin, and its metabolite is a weak μ-opioid receptor agonist.[10] Tramadol and its various formulations (single drug or combined with APAP; immediate-release [IR] or extended-release [ER]) have demonstrated efficacy in the treatment of OA.[10-12] In a study of patients with OA of the knee taking 1,000 mg of the NSAID naproxen, the addition of 200 mg of tramadol made it possible to reduce the naproxen dose by 78% in naproxen-responsive patients without compromising pain relief.[10] In another study, tramadol in combination with APAP was shown to be safe and effective in older patients experiencing breakthrough flares of OA pain.[12] Tramadol can be prescribed for patients in whom nonselective and COX-2–selective NSAIDs are contraindicated or ineffective, and the NSAID dose can be reduced (or discontinued) when tramadol is used without compromising pain relief.

Topical treatments for OA include capsaicin cream, the 5% lidocaine patch, and topical NSAIDs such as diclofenac.[2,13,14] Capsaicin has been shown to be effective in OA of the knees and the small joints of the hands and is indicated for patients who have local pain and cannot tolerate systemic treatments.[15] Derived from pepper plants, capsaicin produces relief from allodynia and joint pain, purportedly by its effect on vanilloid receptors and by the depletion of substance P in peripheral sensory neurons.[16] Use may be limited by intolerable burning pain of the skin, and patients need to be cautioned to keep capsaicin away from mucous membranes, especially those of the eyes.

In Reig's stepladder for the management of rheumatic pain, the use of opioids, such as morphine (Figure 2)[17] and fentanyl, is suggested for severe pain that is not relieved by tramadol, NSAIDs, APAP, and/or other adjuvant analgesics.[6] The American Geriatrics Society guidelines recommend opioids for patients who have moderate to severe pain that cannot be controlled with tramadol.[18] Opioids are a reasonable choice when patients have severe, unrelenting pain and are not candidates, or choose not to be candidates, for joint replacement surgery. Roth and colleagues[19] found that oxycodone CR was an effective

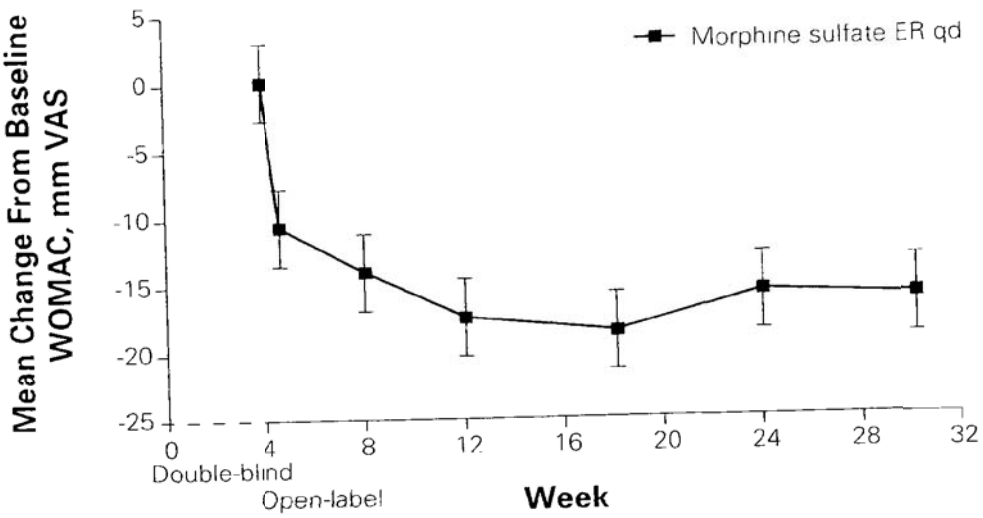


Figure 2. Morphine: long-term pain relief in osteoporosis.[17]

N=81
* $P \leq 0$ 05 versus baseline (week 4)
VAS, visual analog scale, **WOMAC,** Western Ontario and McMaster Osteoarthritis Index

therapeutic regimen for OA-related pain; further studies have shown similar results for other opioid medications, including codeine.[20,21] Typical adverse effects of opioids include constipation, nausea, vomiting, hypogonadism, and mental clouding, which are usually self-limiting or treatable.[22,23] Respiratory depression is very rare when these drugs are titrated slowly.[23]

With the prescription of opioids comes a degree of risk, for both the patient and the physician. The patient must be counseled about harms resulting from misuse and must commit to a treatment plan, and the physician must fulfill legal and regulatory responsibilities. Therefore, as with all drugs, risk assessment should be part of the patient's initial evaluation and should continue throughout the treatment period.

One tool that can aid in this process is the ORT,[24] which is used before opioids are prescribed to stratify patients based on their risk for future aberrant behaviors. This short questionnaire (Chapter 1, Figure 3, page 10), which has been preliminarily validated in terms of specificity and sensitivity, asks patients about several known risk factors for opioid misuse, including personal and family histories of substance abuse and the presence of psychological disorders. Based on their answers,

patients are assigned a gender-specific score classifying them as low-risk, moderate-risk, or high-risk. In a study of 185 patients with chronic pain, Webster and Webster[24] observed that 94.4% of patients categorized as "low-risk" with the ORT did not display aberrant behavior and that 90.9% of patients classified as "high-risk" displayed aberrant behaviors. The stratification of patients based on risk can be used to structure therapy with a suitable level of monitoring and appropriate referrals, if necessary.[25]

Interventional procedures, including intra-articular corticosteroid injections and viscosupplementation with hyaluronans, are options for treating OA pain in certain cases, such as when oral pharmacotherapy is contraindicated or has failed, nonpharmacologic therapies have been ineffective, or adjunctive care is needed.[26] Intra-articular injections of corticosteroids generally offer fast relief of symptoms, but the relief may be short-lived, and frequent injections are often required, which may damage cartilage. There is also concern over potential adverse events such as anaphylaxis and post-injection flare. Viscosupplementation takes advantage of high-molecular-weight hyaluronans such as sodium hyaluronate and hylan G-F 20. It is believed that supplementation with hyaluronans may relieve OA pain by increasing the viscosity of synovial fluid in osteoarthritic joints while reducing the degeneration of native hyaluronans and other key components of cartilage and synovium. Adverse effects of viscosupplementation generally include injection site inflammation, joint effusion, arthralgia, and joint warmth.

Patients such as Juan may experience adequate pain relief while at rest but may need to seek additional treatment for acute flares or incident-type BTP episodes that occur with weight bearing and movement of the joint.[27] Weight is borne on the shoulders during recumbency, so among patients with shoulder OA, pain commonly increases at night and interferes with sleep.

Interestingly, in Juan's case, the physician chose to begin opioid therapy with an LAO rather than select an SAO and switch after titration to an effective dose. Acceptance of this strategy is increasing in the pain management community; identifying those patients who would benefit from LAO treatment and giving them low doses at the onset of therapy may avoid potentially problematic effects of inconsistent analgesia that can result from frequent dosing with SAOs. In this

case, the patient's underlying condition required surgery, but in others, the LAO may provide consistent pain relief sooner than can be achieved by starting with an SAO and switching later

Conclusion

OA is the most common joint disorder and pain-producing problem associated with aging. Treatment goals should include pain relief as well as improvement in function and QoL. A comprehensive management approach that includes nonpharmacologic and pharmacologic therapy and addresses the psychosocial needs of patients is highly beneficial. In Juan's case, a combination of exercise, joint replacement surgery, and an SAO proved most effective

References

1. Arden N, Nevitt MC. Osteoarthritis: epidemiology. *Best Pract Res Clin Rheumatol.* 2006;20(1):3-25.
2. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum.* 2000;43(9):1905-1915.
3. Schiødt FV, Rochling FA, Casey DL, Lee WM. Acetaminophen toxicity in an urban country hospital. *N Engl J Med.* 1997;337(16):1112-1117.
4. Sandler DP, Smith JC, Weinberg CR, et al. Analgesic use and chronic renal disease. *N Engl J Med.* 1989;320(19):1238-1243.
5. Pincus T, Koch G, Lei H, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis.* 2004;63(8):931-939.
6. Reig A. Tramadol in musculoskeletal pain—a survey. *Clin Rheumatol.* 2002; 21(suppl 1):S9-S12.
7. Scott DL, Berry H, Capell H, et al. The long-term effects of non-steroidal anti-inflammatory drugs in osteoarthritis of the knee: a randomized placebo-controlled trial. *Rheumatology (Oxford).* 2000;39(10):1095-1101.
8. Ding C. Do NSAIDs affect the progression of osteoarthritis? *Inflammation.* 2002;26(3):139-142.
9. Ray WA, Chung CP, Stein CM, et al. Risk of peptic ulcer hospitalization in users of NSAIDs with gastroprotective cotherapy versus coxibs. *Gastroenterology.* 2007;133(3):790-798.
10. Schnitzer TJ, Kamin M, Olson WH. Tramadol allows reduction of naproxen dose among patients with naproxen-responsive osteoarthritis pain: a randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 1999; 42(7):1370-1377.

11. Babul N, Noveck R, Chipman H, Roth SH, Gana T, Albert K Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee *J Pain Symptom Manage* 2004;28(1) 59-71

12 Rosenthal NR, Silverfield JC, Wu S-C, Jordan D, Kamin M Tramadol/acetaminophen combination tablets for the treatment of pain associated with osteoarthritis flare in an elderly patient population *J Am Geriatr Soc* 2004, 52(3).374-380

13 Baer PA, Thomas LM, Shainhouse Z Treatment of osteoarthritis of the knee with a topical diclofenac solution. a randomised controlled 6-week trial [ISRCTN53366886] *BMC Musculoskelet Disord* 2005 Aug 8;6:44

14 National Pharmaceutical Council (NPC) and Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Pain current understanding of assessment, management, and treatments December 2001 http://www reliefinsite.com/downloads/Pain_Current_Understanding_of_Assessment_Management_and_Treatment_JCAHO.pdf. Accessed January 8, 2008

15 Zhang W, Moskowitz RW, Nuki G, et al OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines *Osteoarthritis Cartilage* 2008,16(2):137-62

16 Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ.* 2004, 328(7446):991.

17 Caldwell JR, Rapoport RJ, Davis JC, et al Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage.* 2002,23(4).278-291

18 American Geriatric Society. The management of chronic pain in older persons: AGS Panel on Chronic Pain in Older Persons. *J Am Geriatr Soc* 1998, 46(5):635-51.

19. Roth SH, Fleischmann RM, Burch FX, et al Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. *Arch Intern Med.* 2000;160(6):853-860.

20. Caldwell JR, Hale ME, Boyd RE, et al Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial *J Rheumatol.* 1999,26(4): 862-869.

21 Peloso PM, Bellamy N, Bensen W, et al Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol.* 2000,27(3):764-771

22 Ruan X Drug-related side effects of long-term intrathecal morphine therapy. *Pain Physician* 2007(2):357-366.

23 McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain a systematic review *J Pain.* 2003,4(5):231-256.

24. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med.* 2005;6(6):432-442.

25. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med.* 2005;6(2):107-112.

26. Neustadt DH. Intra-articular injections for osteoarthritis of the knee. *Cleve Clin J Med.* 2006;73(10):897-898, 901-904, 906-911.

27. Bennett D, Burton AW, Fishman S, et al. Consensus panel recommendations for the assessment and management of breakthrough pain. Part 1. Assessment. *Pharmacol Ther.* 2005;30(5):296-301. Part 2. Management. *Pharmacol Ther.* 2005;30(6):354-361.

Chapter 3: Martin

A Patient With Pancreatic Cancer

Case

Martin, a 60-year-old man, presents to his PCP with disabling abdominal and thoracic spinal pain that has steadily increased during the past month. He describes the pain as severe most of the time, rating it as 6/10 at its mildest and 9/10 at its worst. The pain worsens with almost all activity and awakens him from sleep but is partially relieved when he lies on his left side. Martin also notes that he has little appetite and has involuntarily lost 42 lb during the past several months.

Current Medications

Martin has been using OTC medications, APAP (1,000 mg 2 or 3 times daily) and ibuprofen (200 or 400 mg 3 times daily), for the pain with little effect. He is also taking glyburide 2.5 mg orally twice daily.

Medical History

Martin's medical history includes type 2 DM.

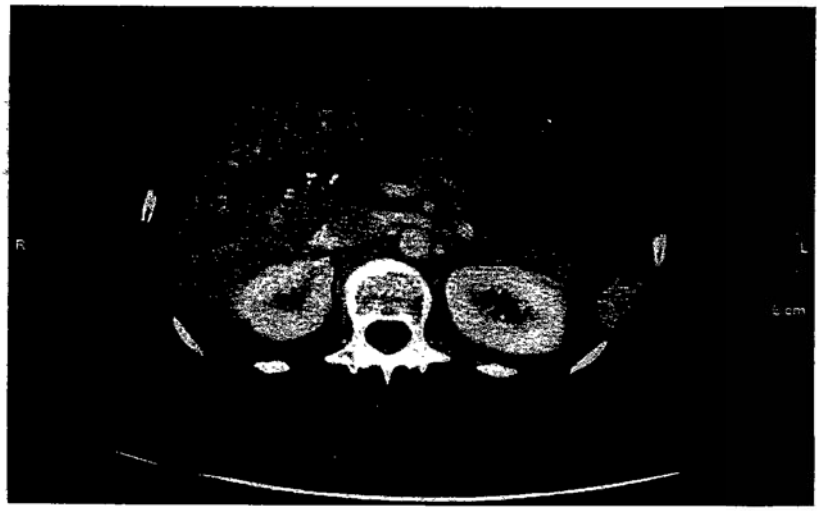


Figure 1. Computed tomography scan showing multiple malignant masses in Martin's pancreas and liver.

Family History

Martin's father died of pancreatic cancer

Social History

Martin is married with 4 children and 2 grandchildren and works as a stockbroker. He is a long-time cigarette smoker (1 pack per day for 40 years) He states that he drinks alcoholic beverages occasionally, but now any alcohol intake greatly exacerbates his pain.

Examination and Diagnosis

Vital signs are normal: BP, 126/85 mm Hg, HR, 77 beats/min; respiratory rate (RR), 17 breaths/min; temperature, 98.6°F. Pain intensity level is 8/10. Pertinent findings on his physical examination reveal a man in obvious distress Abdominal examination demonstrates an enlarged liver, ascites, palmar erythema, spider angiomata, and left supraclavicular lymphadenopathy (Virchow's node). He is mildly jaundiced, but there is no scleral icterus.

Laboratory testing reveals elevated levels of serum bilirubin, alkaline phosphatase, and serum tumor marker cancer antigen (CA) 9-19, suggesting a diagnosis of pancreatic cancer. Dual-phase helical computed tomography (CT) reveals multiple masses in the pancreas and liver (Figure 1). A fine-needle aspiration biopsy specimen confirms the presence of stage IVB pancreatic cancer. Martin is referred to an oncologist for further care.

Treatment and Management

Because his cancer is at such an advanced stage, Martin is considered a poor candidate for surgical resection of his tumors or for radiation therapy. He agrees to a trial of chemotherapy. His oncologist prescribes 7 weekly infusions of gemcitabine at a dose of 1,000 mg/m^2 to moderate tumor growth, reduce the intensity of his pain, and optimize QoL as a palliative measure. Grade 4 hematologic toxicity (marked by neutropenia and anemia) develops after the third infusion, and the drug is discontinued. For his pain, he undergoes endoscopic ultrasonic celiac plexus neurolysis, which is only partially effective. It is clear that Martin requires opioid treatment, as his pain is severe and disabling. The oncologist discusses the risks associated with these agents and asks Martin to ensure that his medication

is kept in a safe place. She prescribes hydromorphone IR 2 to 4 mg every 4 hours as needed.

At a follow-up appointment, Martin states that although his overall daily level of pain is lower with 24 mg of hydromorphone per day, it escalates approximately 3 hours after each dose. His oncologist suspects that he is experiencing end-of-dose failure due to inadequate ATC analgesic coverage. She therefore recommends a switch to a longer-acting opioid formulation to help provide continuous relief. The oncologist starts Martin on the transdermal fentanyl patch at a dose of 50 mcg/h, with the patch changed every 72 hours. This dose is determined by following equianalgesic conversion tables, which approximate the dose of an analgesic medication equivalent in pain-relieving potential to the dose of another analgesic drug. After 2 weeks, Martin notes continued high levels of pain, and his physician increases the dose to 75 mcg/h, changed every 72 hours.

Martin experiences marked relief, with a baseline pain intensity level of 4/10 most of the time. After the fourth week of treatment, he experiences increasingly frequent episodes of severe abdominal and back pain, especially after ingesting any food or drink; however, some episodes occur spontaneously, without warning or evident cause. The BTP is rated at 9+/10, peaks within 15 to 20 minutes, and persists for periods that range from 30 to 90 minutes. This change in his pain pattern prompts Martin to return to his oncologist.

The oncologist decides that Martin requires an additional medication to alleviate the BTP, and after discussing the benefits and risks of ROOs, she prescribes OTFC 200 mcg up to 4 times daily as needed and tells Martin to use the medication before meals and as soon as he feels the onset of a "spontaneous" pain flare. One week later, Martin calls the oncologist to report that the OTFC is "just taking the edge off," and that he is still debilitated by the BTP. The oncologist increases the dose to 400 mcg up to 4 times daily. After 2 weeks of this treatment, Martin's baseline persistent pain remains well controlled, and his treated episodes of BTP are bearable, although still severe at times.

Martin, however, worries that his young grandchildren will mistake the OTFC preparation he keeps at home for lollipops; he is concerned about using OTFC in their presence, and no less self-conscious about sucking on what looks like a lollipop while in public. The physician switches him to FBT, a different ROO, at one-half the dose of the

OTFC he was using because of the greater bioavailability of fentanyl in the FBT formulation. Like OTFC, FBT has a rapid onset of action, but it is formulated as a tablet rather than a lozenge on a stick. Martin's pain remains under control while he takes FBT.

Until the terminal stage of his disease, Martin continues to use transdermal fentanyl for baseline persistent pain plus FBT for BTP When his life expectancy appears to be weeks to months, he is referred for hospice care, in which other analgesic approaches, including parenteral treatment, are required during his final days

Discussion

Pancreatic cancer is a model for the palliative and supportive care of patients with cancer.[1] As the fourth leading cause of cancer deaths in the United States, this disease has a 5-year relative survival rate of just 4%.[2] Estimates prepared by the American Cancer Society for 2008 predict that 37,680 cases will occur in the United States and that 34,290 people will die of the disease.[3] Regardless of stage, pancreatic cancer generally responds poorly to chemotherapeutic, radiologic, and surgical treatment.

The pain associated with pancreatic cancer may be constant or intermittent,[4] and management can pose an ongoing challenge.[5] Between 75% and 80% of patients with pancreatic cancer report pain at their initial presentation, and 10% report severe pain.[5]

Pain syndromes associated with pancreatic cancer result from the proximity of the pancreas to the duodenum, liver, stomach, and jejunum and the interaction of the neural networks that innervate the pancreas with the parasympathetic and sympathetic nervous systems. Patients may experience pain at multiple local and distant sites. Pain attributable to the body of the pancreas can be experienced as midepigastric discomfort, whereas pain attributable to the tail of the organ can be perceived in the left epigastrium and left intercostal space.[6] The pain typical of locally advanced pancreatic cancer, which results from tumor invasion of the celiac and mesenteric plexi and is characterized as neuropathic and inflammatory pain of visceral origin, is dull, often continual, and perceptible in the midback.[5] Pain can also be referred to other structures in the absence of tumor infiltration of somatic nerves. Patients with liver metastasis may report pain in the right shoulder or neck that is referred from sensitive nociceptive areas

within the liver capsule and biliary tract.[6] Other reported pain may be the result of blockage of the pancreatic duct and obstructive and inflammatory pancreatic insufficiency.[5]

A smoker with DM and a family history of pancreatic cancer, Martin has some of the most prominent risk factors for this disease.[2] Others include chronic pancreatitis and alcoholic cirrhosis.[2,7] Classic symptoms of pancreatic cancer include epigastric abdominal pain, weight loss,[8] impaired glucose tolerance, and jaundice that results from obstruction of the common bile duct. Symptoms, including pain, occur as a result of tumor mass rather than disruption of exocrine or endocrine function.[8]

Strategies for the management of pancreatic cancer pain include the use of opioid analgesics; radiation therapy, chemotherapy, and/or celiac plexus neurolysis; and biliary decompression, which can relieve biliary obstructive symptoms.[8] The effects of pain management should be assessed at each encounter with the patient; the 4 A's of monitoring pain treatment can help to maintain function and control pain.[9] Early referral for celiac plexus block is recommended before extensive regional spread of disease, which may prevent effective neural blockade as neural structures become "encased" in tumor.

According to the National Cancer Institute, pain related to all types of cancer often goes undertreated or is inadequately managed.[10] For most patients with chronic cancer pain, meaningful pain control can be achieved through appropriate dosing regimens, upward titration of the dose for control of baseline persistent pain and BTP, opioid rotation, and the use of adjuvant analgesics such as antidepressants, anticonvulsants, and corticosteroids.[6] Patients with moderate or more severe cancer pain are likely to require an ATC opioid regimen that includes an LAO plus an SAO or ROO "rescue" medication for BTP.[6]

The treatment of BTP should ideally match the pharmacokinetic and pharmacodynamic profile of the analgesic to the temporal characteristics of the pain episodes. The ROOs most closely fit the profile of Martin's BTP, offering an onset of analgesic effect faster than the 30 minutes common for traditional SAOs.[11,12] It should be noted that studies of ROOs for BTP have shown no correlation between the doses of medications required for baseline pain and those needed for BTP. Thus, the agents used for BTP must be titrated separately, as in Martin's case, rather than calculated based on the total ATC

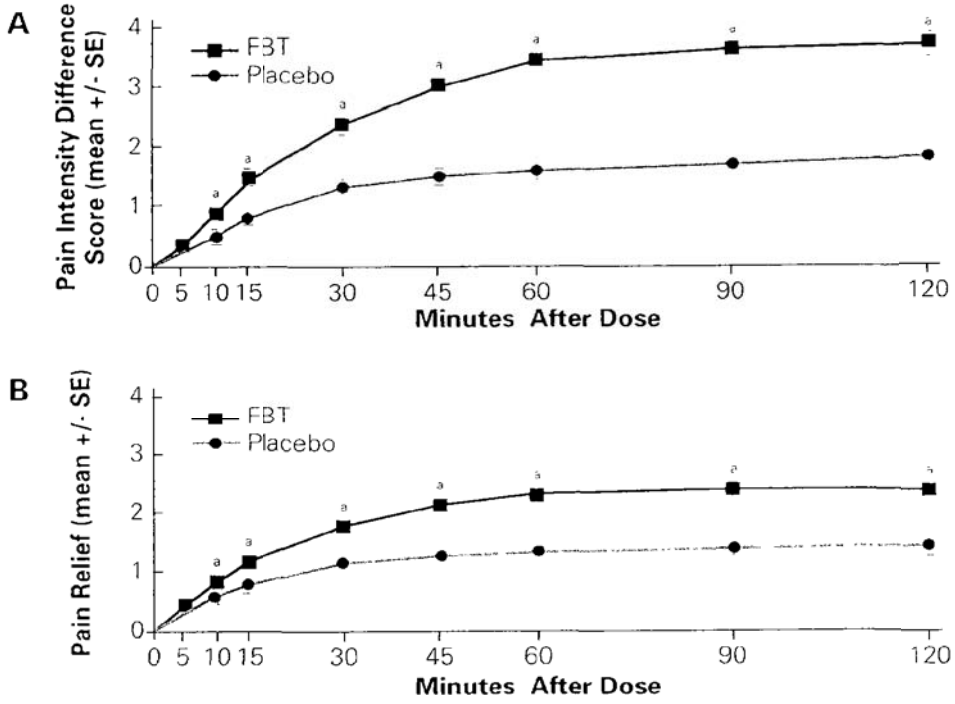


Figure 2. Pain intensity difference and pain relief for FBT and placebo in opioid-tolerant patients (N=78) who have BTP associated with chronic cancer pain.[12]

[a] $P<0.0001$
FBT, *fentanyl buccal tablet,* **BTP,** breakthrough pain

opioid dose.[13]

A recent double-blind, randomized, placebo-controlled study that evaluated the use of FBT corroborated the efficacy of ROOs, showing that FBT is effective and well-tolerated in opioid-tolerant patients with chronic cancer pain (see Chapter 1 for a discussion of opioid tolerance).[12] The absolute bioavailability of FBT is higher than that of OTFC, with more fentanyl absorbed transmucosally from FBT than from OTFC (48% vs 22%).[14] FBT works quickly; for example, it has demonstrated rapid efficacy (as early as 10 minutes after treatment) in cancer-related BTP (Figure 2).[12,15]

Regardless of the type of cancer, a patient's participation in collaborative care and shared decision making can improve outcomes.[16] Comprehensive pain management should respond to the patient's current needs, with sufficient flexibility to respond to changes in health status,

personal preferences and circumstances, and stage of disease.[10] This is particularly critical for the management of pain in patients such as Martin when their disease reaches a stage at which palliative care is the only treatment option.

Conclusion

Pancreatic cancer, which is often diagnosed at advanced stages, responds poorly to chemotherapeutic, radiologic, and surgical treatments and is associated with progressively worsening pain. Opioids are the cornerstone of pain care and can be used along with a spectrum of palliative measures, including radiation, chemotherapy, and other pharmacologic interventions. Patients such as Martin who experience BTP can be offered ROO preparations that address their individual treatment needs with respect to time to peak intensity and duration of pain.[17]

References

1. Fazal S, Saif MW. Supportive and palliative care of pancreatic cancer *JOP.* 2007;8(2):240-253
2. American Cancer Society *Cancer Facts & Figures 2008* Atlanta, GA: American Cancer Society; 2008. http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf. Accessed March 8, 2008
3. Greenlee RT, Murray T, Bolden S, Wingo PA Cancer statistics, 2000. *CA Cancer J Clin.* 2000;50(1):7-33.
4. Memorial Sloan-Kettering Cancer Center. Pancreatic cancer. symptoms (2003). http://www.mskcc.org/mskcc/html/1039.cfm. Accessed January 3, 2008.
5. El-Kamar FG, Grossbard ML, Kozuch PS Metastatic pancreatic cancer emerging strategies in chemotherapy and palliative care. *Oncologist.* 2003,8(1):18-34.
6. Brescia FJ Palliative care in pancreatic cancer *Cancer Control.* 2004; 11(1):39-45.
7. Ye W, Lagergren J, Weiderpass E, et al Alcohol abuse and the risk of pancreatic cancer. *Gut* 2001;51(2):236-239.
8. Freelove R, Walling AD Pancreatic cancer diagnosis and management *Am Fam Physician.* 2006;73(3) 485-492
9. Passik SD, Weinreb HJ. Managing chronic nonmalignant pain overcoming obstacles to the use of opioids *Adv Ther.* 2000;17(2):70-83

10. National Cancer Institute. Pain (PDQ®) health professional version 2007 http //www nci.nih gov/cancertopics/pdq/supportivecare/pain/healthprofessional/allpages. Accessed January 3, 2008.

11 Zeppetella G, Ribeiro MD Opioids for the management of breakthrough (episodic) pain in cancer patients *Cochrane Database Syst Rev.* 2006, (1) CD004311

12 Slatkin NE, Xie F, Messina J, Segal TJ Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol.* 2007,5(7).327-334

13 Hagen NA, Fisher K, Victorino C, Farrar JT A titration strategy is needed to manage breakthrough cancer pain effectively: observations from data pooled from three clinical trials *J Palliat Med* 2007,10(1) 47-55.

14 Darwish M, Kirby M, Robertson P Jr, Tracewell W, Jiang JG Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol* 2007,47(3):343-350

15 Portenoy RK, Taylor D, Messina J, Tremmel L A randomized, placebo-controlled study of fentanyl buccal tablets for breakthrough pain in opioid-treated patients with cancer *Clin J Pain* 2006,22(9).805-811

16 Gordon DB, Dahl JL, Miaskowski C, et al. American Pain Society recommendations for improving the quality of acute and cancer pain management. American Pain Society Quality of Care Task Force. *Arch Intern Med* 2005,165(14):1574-1580

17 Fine PG. *The Diagnosis and Treatment of Breakthrough Pain* New York, NY Oxford University Press, 2008

Chapter 4: William

A Patient With Low Back Pain

Case

William, a 42-year-old man, reports to his PCP with LBP that has increased in intensity during the past 6 months. The pain began insidiously without a definite triggering incident or traumatic event. It has recently begun to interfere with William's work routine, recreational activities, and family interactions, such that he cannot lift his 2-year-old daughter or be intimate with his wife. The pain occasionally radiates to both buttocks but not beyond. He has no bowel or bladder complaints, loss of strength, or loss of sensation.

Current Medications

William currently takes 650 mg of aspirin 4 to 5 times daily.

Medical History

William is otherwise healthy without any significant medical or surgical history. He was involved in contact sports, including lacrosse and hockey, throughout his youth but never sustained a back injury that required medical attention.

Family History

The patient's family history is noncontributory, although William does recall that his paternal grandparents both had debilitating arthritis in their last few years of life.

Social History

William is married and has a daughter. He is employed as a procurement supervisor and waiter for a catering company, work that entails frequently lifting heavy trays and moving large boxes of food and supplies. He smoked until age 31 but has since quit. He denies any history of substance abuse but reports drinking a few beers occasionally after work. He has no prior history of work-related disability or liability claims.

Examination and Diagnosis

William's physical examination reveals normal vital signs: afebrile; BP, 110/75 mm Hg; HR, 73 beats/min; RR, 17 breaths/min. His general examination is unremarkable; however, his musculoskeletal examination shows significant impairment in forward flexion of the lumbar spine beyond 30 degrees. His pain intensity level, rated as 5/10 at rest, reaches 8/10 when he moves his lumbar spine from even a partially flexed to an extended position. In this position, his spine is particularly tender bilaterally at the L4 and L5 levels. No tenderness is noted over the sacroiliac joints or the greater sciatic notches, and no paraspinal muscle spasm is present.

His neurologic examination, including a gait assessment, reveals no abnormalities.

Several features of the presentation and examination suggest that William's LBP is associated with a lumbar facet arthropathy: his age and job, pain with spinal extension, normal gait, and the absence of leg pain and paraspinal muscle spasms. The physician suspects that several of William's lumbar facet (zygaphophyseal) joints are the source of his pain, and X-ray imaging of the lumbosacral spine confirms the presence of bilateral multilevel degenerative changes in the facet joints (Figure 1).

Treatment and Management

William's physician initially advises the use of diclofenac 75 mg twice daily, tizanidine 4 mg at bedtime as a spasmolytic agent, hydrocodone 5 mg/APAP 500 mg orally 4 times daily for severe pain, and physical therapy. When William returns 1 month later, he reports that the hydrocodone/APAP seems to help him the most but

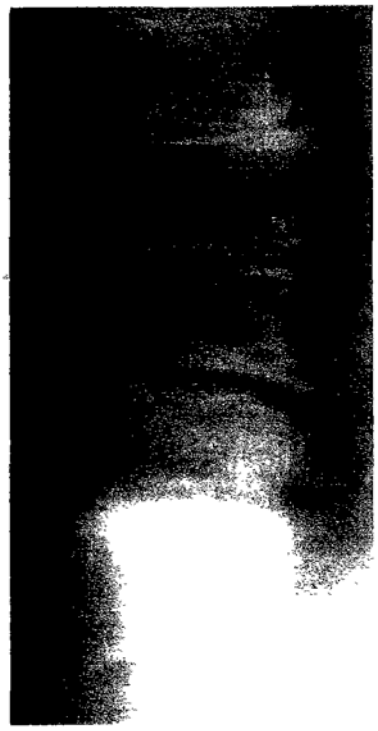


Figure 1. X-ray of William's lumbosacral spine showing degenerative changes in the facet joints.

that he cannot find a comfortable position at night, making sleep difficult even though he feels tired. His physician discontinues the tizanidine and advises a trial of nortriptyline 25 mg at bedtime in addition to the diclofenac and hydrocodone/APAP. William cannot tolerate this regimen because of adverse effects, including dry mouth, constipation, and daytime "grogginess." A report from the physical therapist confirms adherence to the exercise program.

In view of this, the PCP considers prescribing a different opioid. As part of an ongoing assessment to determine whether William is an appropriate candidate for long-term opioid therapy, the PCP administers the SOAPP-R (score, 4) and notes that William has no known personal or family history of substance abuse, has been compliant with physical therapy and the use of nonopioid medications, and is working full-time. Using an equianalgesic conversion table to help calculate the appropriate dose, William's physician prescribes an LAO, morphine ER, titrated up to 60 mg once daily.

At follow-up, William reports some relief of his pain with the morphine but also a lack of mental clarity at times, which makes him feel incompetent at work. Feeling mentally "fuzzy," he cannot remember things like customers' drink orders, and he fears that his job may be in jeopardy. William's PCP advises him to discontinue the morphine and switches him to the transdermal fentanyl patch at a dose of 25 mcg/h, changed every 72 hours. The side effects do not decrease. William wants to return to his normal mental state and asks his physician what more can be done. William also admits fearing that he will be "crippled up in pain" as his grandparents were. His physician refers him to an interventional pain specialist.

The pain specialist suggests that William receive therapeutic facet joint blocks and describes the expectations for outcomes with this treatment. He tapers William's opioid medication and performs the procedure. After the injection, William reports a significant decrease in pain without serious side effects. His baseline pain intensity level is now at 3/10, but William still experiences bursts of increased pain at a level of 5-6/10 when he unloads the catering truck in the morning. William's doctor advises him to take 1,000 mg of APAP before any heavy lifting to prevent the episodes of incident BTP; this sufficiently controls the pain. In addition, he has been advised to maintain a disciplined program of flexibility and strengthening exercises, and

to "check in" on a monthly basis for 3 months with the physical therapist, both to evaluate his progress and to reinforce his self-directed program of back care

Discussion

LBP is the fifth most common reason for physician visits in the United States.[1] Approximately 70% to 85% of the US population will experience LBP during their lifetime, and approximately 2% of the work force is compensated for back injuries each year.[1-4]

William's pain can be classified as having a "mechanical" cause, meaning that it arises from trauma or an anatomic abnormality. In William's case, the pain is associated with heavy lifting at work. Mechanical causes account for the overwhelming majority of instances of LBP.[5-8] In most cases, LBP interferes only temporarily with patient function and is not disabling; in fact, in 80% to 90% of patients, the problem completely resolves within 12 weeks of onset.[4] In some cases, however, the condition is recurrent or persistent and results in chronic pain. Those cases that become chronic present most of the treatment challenges and incur most of the health care costs associated with LBP.[1] The prognosis worsens as the duration of pain increases, with patients' chances of returning to work after being on disability for more than 2 years diminishing to less than 5%.[4,9]

In most chronic cases, the exact biological cause of LBP is not evident (Table 1, page 48).[2,5-8,10] If thorough testing to identify any lingering injury or disease proves unsuccessful, the therapeutic goals become pain control and restoration of function to maximize QoL.[11]

William's condition was diagnosed as lumbar facet arthropathy. This diagnosis can arise from any number of causes, such as rheumatoid arthritis, small fractures from recurrent trauma, and osteoarthritis. In William's case, genetic predisposition coupled with years of contact sports and a physically taxing job are likely causes of this common condition. Studies of the prevalence of lumbar facet joint pain have been inconclusive, although facet joints have been implicated as the source of chronic pain in 10% to 15% of patients with chronic LBP.[12]

Patients with lumbar facet joint pain typically present with mechanical LBP that radiates to the buttocks and upper posterior thigh. The most reliable means of diagnosing facet joint–mediated pain is a controlled diagnostic block; however, this is impractical in a clinical

Table 1. Diagnostic Studies Commonly Used in the Evaluation of Low Back Pain[10]

Imaging Tool	Comments
Spinal plain films	Low specificity and predictive value
Computed tomography (with myelography)	Demonstrates >90% of herniated disks, but can yield false-positive results
Magnetic resonance imaging	Excellent soft-tissue and disk images
Thermography	Can be used for confirmation of autonomic dysfunction in conditions such as reflex sympathetic dystrophy
Electromyography and nerve conduction studies	Objectively assesses severity, location, and extent of nerve and muscular lesions
Laboratory tests	Useful for screening for infection, tumor, or nonspinal causes of low back pain

setting. An uncontroled diagnostic block may be helpful, but investigators have identified high rates of false-positive results with this methodology and suggested its benefits are limited.[13]

Potentially effective nonpharmacologic therapies for the treatment of LBP include CBT, exercise, and massage. Each of these techniques has been shown to aid recovery and elevate mood in clinical trials.[14-19] There is strong evidence that anxiety and depression are correlated with the transition from acute to chronic LBP conditions, so behavioral approaches that improve mood may also improve the prognosis.[4,20] The goal of CBT is to give patients a perception of greater control of their situation and to improve their outlook regarding their progression in therapy by altering psychological processes.[21] Various studies have shown that although CBT techniques provide short-term relief from LBP, their long-term effects on pain and functional status when used alone or in conjunction with other therapies are unclear.[16] Nonetheless, in the absence of pathologic lesions that present a risk for fracture or neurologic damage, patients with LBP must learn *not* to

feel particularly vulnerable or to interpret pain as a sign of weakness or fragility.

Exercise and massage have proved modestly beneficial in relieving symptoms of LBP, improving function, and promoting the release of endorphins to elevate mood.[14] Weight loss through exercise and dietary changes can decrease demands on the spine, reduce further exacerbation of an injury, and improve health in general. Although a correlation exists between LBP and smoking, the mechanism for the connection is not clear; hypotheses implicate the detrimental effects of smoking on general health and the confounding factors commonly associated with smoking, such as depression and unhealthy lifestyles, although recent reviews of the effects of smoking on the development of LBP have failed to identify a reliable relationship between them.[22]

Nonpharmacologic treatment options should be implemented along with medical therapies because multidisciplinary treatment strategies, emphasizing a biopsychosocial approach to pain management, have shown higher success rates than have approaches based on a single modality.[23]

Interventional procedures commonly performed for facet joint pain include intra-articular injections, medial branch blocks, and radiofrequency neurolysis of medial branch nerves. These and other interventions for chronic LBP, such as epidural injections, facet joint injections, and nerve root blocks, have been performed by pain specialists for many years.[24,25] Initially, blocks were performed by palpating anatomic landmarks and administering steroids and/or local anesthetics. As techniques have been refined, fluoroscopic and CT guidance have increasingly been used during the performance of these injections to assist in more precise needle placement and drug deposition. Typically, facet joint injections are included as part of a workup or treatment for back or neck pain. Because many patients do not have a readily identifiable cause of pain based on imaging studies and clinical evaluation, various injections are often performed to try to localize the "pain generator." This process may include facet injections, epidural injections, selective nerve root blocks, and in certain patients, diskography. There are no methodologically sound prospective outcome studies either to guide this process or to determine its overall effectiveness.[26]

Pharmacologic treatment options for LBP include topical agents, APAP, NSAIDs, muscle relaxants, antidepressants, and opioid analgesics.[27-33] Following a physical examination and a thorough patient history, NSAIDs are recommended as first-line treatment.[11,34] Muscle relaxants may be added if there is a muscular component to the pain and a muscle spasm is palpable on examination. Although NSAIDs and muscle relaxants effectively control acute LBP, there is very little evidence that either of these treatment modalities is successful for chronic LBP.[11,27] NSAIDs also are associated with potentially serious adverse events, including an increased risk for thrombotic cardiovascular or cerebrovascular disease (COX-2–selective agents), GI toxicity, disturbances in renal function, increases in blood pressure, hepatic injury, and (except for the nonacetylating agents and COX-2–selective drugs) platelet inhibition leading to increased risks for bleeding.[35]

If NSAIDs and muscle relaxants do not provide sufficient analgesia, a tricyclic or tetracyclic antidepressant may be prescribed.[29] These agents, however, also are associated with high rates of side effects, such as dry mouth, constipation, urinary retention, orthostatic hypotension, insomnia, and sedation. Treatment must therefore be monitored to weigh the benefits against the risks experienced by each patient. If analgesia is still insufficient, opioid treatment should be considered.

Opioids are among the most commonly prescribed and studied treatments for LBP and have proved efficacious in numerous studies conducted with placebo or nonopioid controls.[36-42] A literature review and meta-analysis suggested that opioid analgesic therapy provides short-term pain relief for patients with chronic LBP, but that randomized clinical trial evidence for long-term benefits is lacking.[43,44] In a 1-year study designed to compare the analgesic effects of NSAIDs with those of opioids in 36 patients who had LBP, the opioid-treated patients showed less pain and emotional distress than the patients treated with NSAIDs.[32] No difference, however, was noted for activity or sleep. Patients receiving opioids reported moderate levels of pain during treatment but were reluctant to increase their opioid doses because of side effects.[32] In comparison with NSAIDs, opioids proved superior in pain relief, but not adverse events.[32]

Many physicians are hesitant to prescribe opioids because of adverse events and the risk for misuse. For William, the PCP administered the

SOAPP-R, a short questionnaire that can help determine how much monitoring is required for patients with chronic pain who are candidates for long-term opioid therapy.[45] Developed to assess the level of risk regarding aberrant medication-related behaviors, the original SOAPP included 24 items, 14 of which were found to predict self-reported problematic behaviors related to opioid use. The SOAPP-R is an empirically derived revision that includes 24 items and psychometric values (8 of which were included in the original version).[46] Patients assign a score of 0 (never) to 3 or 4 (very often) to each item, with a total score of 18 or higher identifying those at high risk for aberrant behaviors. The revised version was validated in 283 patients with chronic pain; the threshold score identified 80% of the patients who were later confirmed to be at high risk, as determined by self-report, UDT, and physician report.

Physicians also should consider the possibility that an opioid trial will fail and frame a strategy for discontinuing the use of that particular opioid should the patient exhibit insufficient gains in analgesia and function, intolerable adverse events, or noncompliance with the treatment agreement.[47] Lack of efficacy should prompt consideration of a different opioid (opioid rotation) or route of administration. When adherence to the treatment plan proves problematic or the goals of therapy are not being met, increasing the therapeutic and monitoring parameters (ie, more tightly structuring therapy) should be considered. If discontinuation of opioids as a class is indicated, the medication should be tapered to avoid withdrawal symptoms.

A recent systematic review of published studies of opioid treatment for LBP showed that aberrant drug-taking behaviors occurred at a rate of 5% to 24%.[44] However, if patients and physicians agree on a course of treatment, move through a carefully planned dose titration period, and maintain frequent monitoring for signs of aberrant behaviors, opioid therapy can successfully provide many patients with analgesia and improve their QoL.[38-42]

Conclusion

Chronic LBP is often difficult to diagnose and treat. A number of nonpharmacologic and pharmacologic treatment options are recommended for LBP, including opioid analgesics. Before an opioid trial, the expectations and goals of treatment must be clearly defined. Although opioids are well tolerated by many patients, they may cause

unacceptable adverse events, such as cognitive side effects, in others. In such cases, opioid rotation is a possibility, although some patients may not tolerate opioids at all. Interventional treatments provide another series of treatment options. In William's case, a combination of therapeutic facet joint blocks and prophylactic APAP for incident BTP, coupled with an active physical therapy program, provided adequate relief and confidence in recovery.

References

1. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med.* 2007;147(7):478-491.
2. Deyo RA, Weinstein JN. Low back pain. *N Engl J Med.* 2001;344(5):363-370.
3. van Tulder M, Koes B. Chronic low back pain. *Am Fam Physician.* 2006;74(9):1577-1579.
4. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet.* 1999;354(9178):581-585.
5. Hart LG, Deyo RA, Cherkin DC. Physician office visits for low back pain. frequency, clinical evaluation, and treatment patterns from a U.S. national survey. *Spine.* 1995;20(1):11-19.
6. Deyo RA. Early diagnostic evaluation of low back pain. *J Gen Intern Med.* 1986;1(5):328-338.
7. Deyo RA, Rainville J, Kent DL. What can the history and physical examination tell us about low back pain? *JAMA.* 1992;268(6):760-765.
8. Deyo RA, Diehl AK. Cancer as a cause of back pain: frequency, clinical presentation, and diagnostic strategies. *J Gen Intern Med.* 1988;3(3):230-238.
9. van den Hoogen HJ, Koes BW, van Eijk JT, Bouter LM, Deville W. On the course of low back pain in general practice: a one year follow up study. *Ann Rheum Dis.* 1998;57(1):13-19.
10. Grabois M. Management of Chronic Low Back Pain. *Am J Phys Med Rehabil.* 2005;84(suppl):S29-S41.
11. Diamond S, Borenstein D. Chronic low back pain in a working-age adult. *Best Pract Res Clin Rheumatol.* 2006;20(4):707-720.
12. Cohen SP, Raja SN. Pathogenesis, diagnosis, and treatment of lumbar zygapophysial (facet) joint pain. *Anesthesiology.* 2007;106(3):591-614.
13. Schwarzer AC, Aprill CN, Derby R, et al. Pain from the lumbar zygapophysial joints: a test of two models. *Pain.* 1994;58(2):195-200.
14. Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. *Cochrane Database Syst Rev.* 2005;(3):CD000335.

15 Mannion AF, Muntener M, Taimela S, et al Comparison of three active therapies for chronic low back pain results of a randomized clinical trial with one-year follow-up *Rheumatology (Oxford)* 2001;40(7) 772-778

16 Furlan AD, Brosseau L, Imamura M, Irvin E. Massage for low-back pain a systematic review within the framework of the Cochrane Collaboration Back Review Group. *Spine* 2002,27(17)·1896-1910

17 Ostelo RW, van Tulder MW, Vlaeyen JW, Linton SJ, Morley SJ, Assendelft WJ Behavioral treatment for chronic low-back pain. *Cochrane Database Syst Rev* 2005,(1)·CD002014

18 Deyo RA, Bass JE. Lifestyle and low-back pain The influence of smoking and obesity. *Spine*. 1989;14(5).501-506

19 Chou R, Huffman LH, American Pain Society, American College of Physicians. Medications for acute and chronic low back pain a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007 Oct 2,147(7) 505-14

20. Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine*. 2002,27(5)·E109-E120.

21 Turk DC, Flor H Etiological theories and treatments for chronic back pain II· Psychological models and interventions Pain 1984;19(3).209-233

22. Rubin DI Epidemiology and risk factors for spine pain *Neurol Clin* 2007; 25(2) 353-371

23. Guzman J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C Multidisciplinary bio-psycho-social rehabilitation for chronic low back pain. *Cochrane Database Syst Rev* 2002;(1).CD000963.

24. Carette S, Marcoux S, Truchon R, et al. A controlled trial of corticosteroid injections into facet joints for chronic low back pain *N Engl J Med* 1991; 325(14) 1002-1007

25. Murtagh R The art and science of nerve root and facet blocks. *Neuroimaging Clin N Am* 2000;10(3) 465-477

26 Carragee EJ. Clinical practice. Persistent low back pain *N Eng J Med* 2005;352(18)·1891-8

27. van Tulder MW, Scholten RJ, Koes BW, Deyo RA. Nonsteroidal anti-inflammatory drugs for low back pain. a systematic review within the framework of the Cochrane Collaboration Back Review Group *Spine*. 2000;25(19). 2501-2513

28. Salerno SM, Browning R, Jackson JL The effect of antidepressant treatment on chronic back pain: a meta-analysis. *Arch Intern Med*. 2002;162(1). 19-24

29 Staiger TO, Gaster B, Sullivan MD, Deyo RA Systematic review of antidepressants in the treatment of chronic low back pain *Spine* 2003;28(22) 2540-2545.

30. Mahowald ML, Singh JA, Majeski P Opioid use by patients in an orthopedics spine clinic *Arthritis Rheum*. 2005;52(1).312-321.

31 Schnitzer TJ, Ferraro A, Hunsche E, Kong SX. A comprehensive review of clinical trials on the efficacy and safety of drugs for the treatment of low back pain. *J Pain Symptom Manage*. 2004;28(1):72-95.

32 Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. *Spine*. 1998;23(23):2591-2600.

33 Chou R, Huffman LH, American Pain Society, American College of Physicians. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007 Oct 2;147(7):492-504.

34 Ehrlich GE. Low back pain. *Bull World Health Organ*. 2003;81:671-676.

35 Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res*. 2007;5(1):19-34.

36 Hale ME, Speight KL, Harsanyi Z, Iwan T, Slagle NS, Lacouture PG. Efficacy of 12 hourly controlled-release codeine compared with as required dosing of acetaminophen plus codeine in patients with chronic low back pain. *Pain Res Manag*. 1997;2(1):33-38.

37 Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain*. 1999;15(3):179-183.

38. Kuntz D, Brossel R. Analgesic effect and clinical tolerability of the combination of paracetamol 500 mg and caffeine 50 mg versus paracetamol 400 mg and dextropropoxyphene 30 mg in back pain. *Presse Med*. 1996;25(25):1171-1174.

39. Muller FO, Odendaal CL, Muller FR, Raubenheimer J, Middle MV, Kummer M. Comparison of the efficacy and tolerability of a paracetamol/codeine fixed-dose combination with tramadol in patients with refractory chronic back pain. *Arzneimittelforschung*. 1998;48(6):675-679.

40. Richards P, Zhang P, Friedman M, Dhanda R. Controlled-release oxycodone relieves moderate to severe pain in a 3-month study of persistent moderate to severe back pain. *Pain Med*. 2002;3(2):176.

41. Tennant F, Moll D, DePaulo V. Topical morphine for peripheral pain. *Lancet*. 1993;342(8878):1047-1048.

42 Thurel C, Bardin T, Boccard E. Analgesic efficacy of an association of 500-mg paracetamol plus 30-mg codeine versus 400-mg paracetamol plus 30-mg dextropropoxyphene in repeated doses for chronic lower back pain. *Curr Ther Res*. 1991;50(4):463-473.

43 Bartleson JD. Evidence for and against the use of opioid analgesics for chronic nonmalignant low back pain: a review. *Pain Med*. 2002;3(3):260-271.

44. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007;146(2):116-127.

45 Akbik H, Butler SF, Budman SH, et al. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). *J Pain Symptom Manage* 2006;32(3):287-293

46 Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). *J Pain* 2008;9(4):360-372

47 Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med* 2003; 349(20):1943-1953

Chapter 5: Gordon

A Patient With Complex Regional Pain Syndrome

Case

Gordon, a 38-year-old man, presents with pain related to CRPS. Five years earlier, he was diagnosed with CRPS after a biking accident resulted in a right common peroneal nerve injury. Within weeks of the injury, Gordon experienced excruciating pain, swelling, and discoloration (sometimes bluish, sometimes reddish) in his right leg. Since his diagnosis was made, he has noted that his right leg and foot rarely feel as if they are at a comfortable temperature; rather, they are either icy cold or burning hot. He also feels severe pain whenever anything touches these areas. Subsequently, he has undergone a number of pain management therapies, including nerve blocks, spinal stimulation, and pharmacotherapy with desipramine, tramadol, duloxetine, carbamazepine, and gabapentin. Gordon reports that none of these treatments has sufficiently controlled his pain, and he has stopped using them. He presents to a pain specialist for analgesic alternatives.

Current Medications

Gordon currently takes loratadine 10 mg daily for environmental allergies.

Medical History

During his late 20s, Gordon was treated for depression with fluoxetine. Aside from this disorder and his CRPS, his medical history is unremarkable.

Family History

Gordon's mother has type 2 DM. His family history is otherwise unremarkable.

Social History

Gordon is an airport security guard, and the pain has made him unable to work regularly. He is married with 2 children, a 9-year-old girl

and a 6-year-old boy. His use of alcohol is generally confined to weekends, when he has 4 to 7 drinks with friends. He does not smoke and has no history of substance abuse

Examination and Diagnosis

Vital signs are normal. BP, 112/73 mm Hg; HR, 76 beats/min; RR, 16 breaths/min. The patient is afebrile. His relevant physical examination is notable for edema, tactile allodynia, and hyperalgesia of the right leg and foot. The right leg and foot are clearly cooler than the left (Figure 1). Pulses are intact and deep tendon reflexes are present. Gordon reports his pain as 5/10 at its least and 9/10 at its worst.

Treatment and Management

Gordon's pain has responded poorly to nonopioid analgesics in the past, so the pain specialist suggests an opioid trial. She follows a Universal Precautions approach to prescribing (Chapter 1), which includes assessing the patient's risk for aberrant drug-related behaviors. Gordon receives a score of 2 on the ORT, which places him at low risk for these behaviors. At his physician's request, he also reads and signs a controlled substance agreement (Chapter 1). The physician

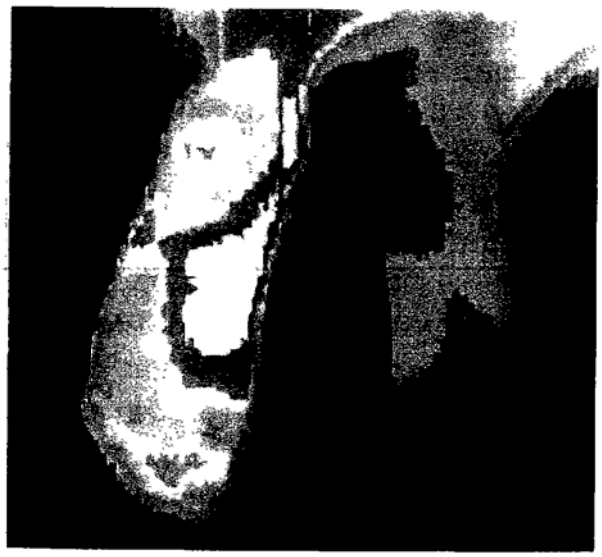


Figure 1. Thermographic image of Gordon's feet showing temperature variation; dark areas indicate cold (~26°C), and lighter areas indicate heat (~32°-33°C).

prescribes oxycodone CR 10 mg every 12 hours and schedules a follow-up appointment 4 weeks later. Before he leaves her office that day, Gordon is asked to give a urine sample, which is sent for UDT; it is negative for any inappropriate substances. She advises him to discontinue all alcohol use until his analgesic regimen has been stabilized. Then, she counsels him to limit his alcohol intake to no more than 1 to 2 oz per evening during his usual weekend social interactions and to discontinue drinking alcohol at least a few hours before going to sleep; the rationale for this advice is to prevent the adverse effects of a combination of opioid, alcohol, and sleep physiology on respiration.

At first, the treatment effectively reduces Gordon's persistent baseline pain to 3-4/10, and he returns to work full-time. However, after a few weeks, he reports that his pain gradually increases toward the end of the workday and becomes very intense by about 6 PM. The physician re-evaluates Gordon and concludes that there is no new medical reason for his pain other than the previously diagnosed CRPS. She notes that the increase in pain occurs daily just before the second dose of his long-acting drug and determines that he is likely experiencing end-of-dose failure. To help reduce this BTP, she increases Gordon's dose of oxycodone CR to 20 mg every 12 hours.

A few weeks later, Gordon's pain begins to bother him again, but this time as flares of severe burning, shooting pain in his leg and foot, rated 8/10, whenever he stands for an extended time. These episodes of incident BTP, which spike to maximum intensity within 15 minutes, often occur at his job, and he begins to worry about what effect they will have on his ability to make a living now that he has finally returned to work. Gordon does not want to miss additional work, so he begins taking extra doses of his long-acting medication on "bad" days. He runs out of his prescription and calls to request an early refill.

The specialist schedules an immediate appointment with Gordon to discuss the situation and reassesses his analgesic regimen: Gordon is again experiencing inadequate analgesia that interferes with his ADLs, and he is displaying the aberrant behavior of self-escalation of dosing. He is not experiencing any adverse effects from the medication. UDT confirms that he is taking the prescribed medication but no other controlled substances.

Gordon admits that he ran out of his prescription early because he increased his daily dose in an effort to ease his pain, and the last time

his pain was not well controlled, the physician had increased his dose. The specialist explains to Gordon that a different strategy may better treat episodes of activity-related BTP and reiterates the terms of the controlled substance agreement, including that Gordon is to call her if his pain is not responding to the medication and not to increase his dose on his own. She also requires that Gordon come in for biweekly follow-up appointments to obtain his refills.

The pain specialist further decides that Gordon requires an additional medication to alleviate these episodes. After discussing the benefits and risks of ROOs, she prescribes OTFC 200 mcg up to 4 times daily as needed and tells Gordon to use the medication as soon as he feels the onset of an episode.

With this new combination of medications and the additional structure of biweekly appointments, Gordon is able to treat both his persistent baseline pain and his BTP adequately while continuing his employment, and his physician is able to monitor his treatment carefully.

Discussion

The pathophysiology of CRPS is unclear,[1] making it a difficult disorder to treat with curative therapies. It generally occurs after some degree of physical trauma; if the trauma leads to identifiable major nerve damage, the condition is referred to as CRPS type II and if not, it is referred to as CRPS type I. CRPS is more common among women than men and affects a relatively young patient population (mean age, 36-42 years).[2] CRPS is distinguished from other pain conditions not only by the type of pain associated with the disease but also by signs of sympathetic nervous system dysfunction in some cases. The pain of CRPS often is characterized as aching, shooting, burning, or pricking. Although pain is the predominant symptom, patients with CRPS also frequently experience hyperesthesia, sweating abnormalities (so-called sudomotor abnormalities), alterations in temperature and skin color, swelling, and weakness.[2] Furthermore, between 24% and 60% of patients report tremor, and between 56% and 61% report myofascial dysfunction.[3]

CRPS is treated with a variety of modalities.[2] Some authors recommend a 3-pronged approach, including functional rehabilitation, pain management (eg, multidrug therapy and interventions), and psychological therapy (Figure 2, page 60).[2] By monitoring how a patient

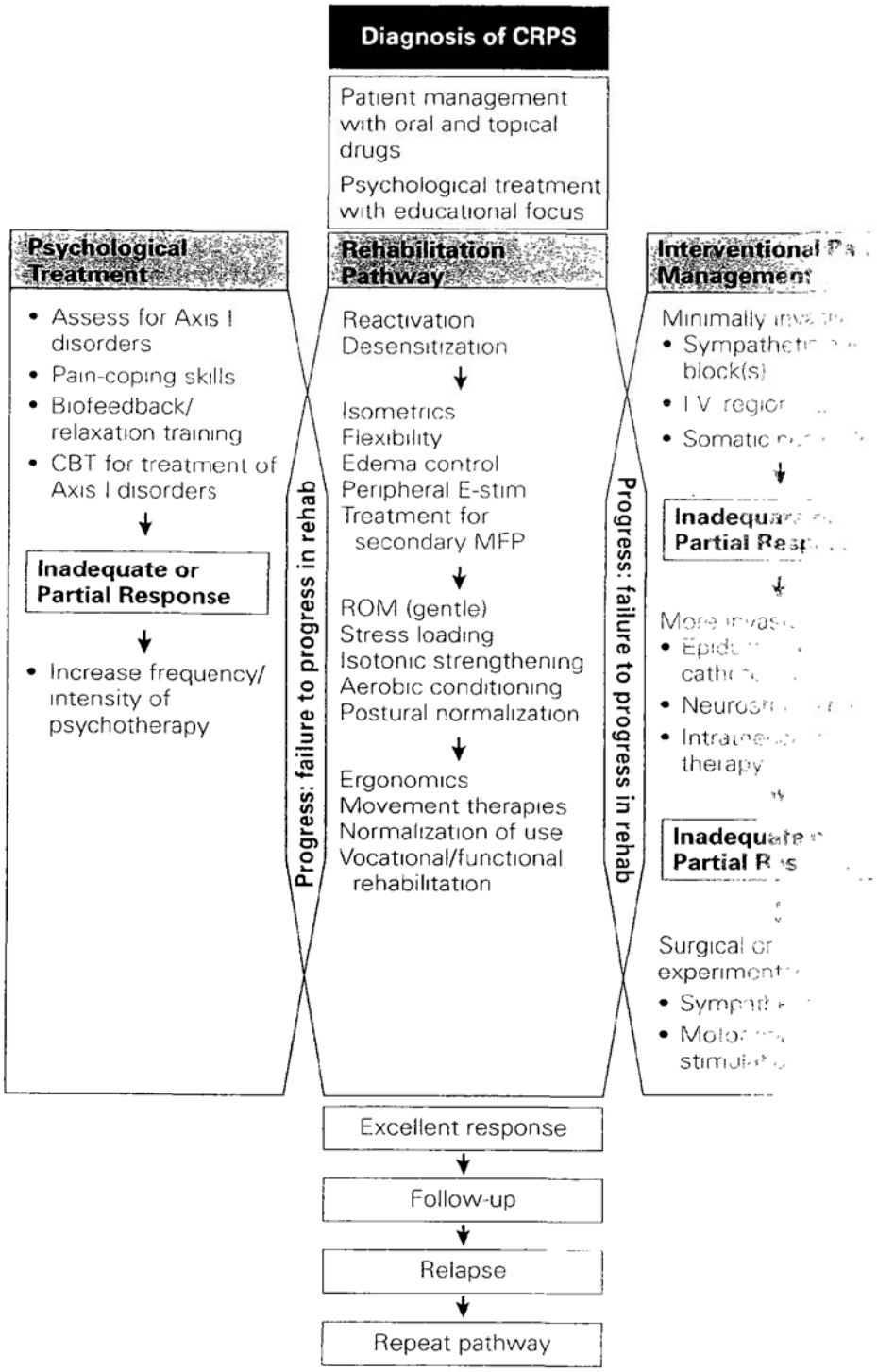


Figure 2. Revised therapeutic algorithm for CRPS

CBT, cognitive-behavioral therapy, **CRPS,** complex regional pain syndrome, E-stim tion, **MFP,** myofascial pain, **ROM,** range of motion

advances in the rehabilitative process, the physician becomes aware of any changes in treatment that may be needed, such as a stronger analgesic or possibly an additional intervention. When approaching pain management, whether nonpharmacologically or through oral, parenteral, transdermal, buccal, or topical pharmacologic routes, both the physician and the patient should maintain flexibility.[4] Ineffective treatment should not be continued; rather, failure of therapy to provide sufficient analgesia should prompt the consideration of other treatments, including nerve blocks, spinal stimulation, and continuous epidural analgesia (continuous injection of an analgesic agent into the epidural space).[5,6] Behavioral approaches to pain reduction, including formal psychotherapy, training in pain coping skills, CBT, and others, may also help to reduce the pain associated with CRPS and improve the patient's overall QoL.[2]

Treatment with opioids requires assessment and management of the risks for abuse. Clarity on these issues should facilitate a more productive discussion of the growing problem of drug misuse in the United States. Gilson et al[7] concluded that 9.85% of all emergency drug-related admissions to hospitals in the United States in 2002 were a result of opioids, up from 5.75% in 1997. Because diversion has legal implications, it is in the physician's best interest to exercise caution when prescribing medication. This can be accomplished by establishing a system to assess and monitor each patient for the risk for medication misuse.

Gordon's initial ORT score is 2, suggesting that opioids should be considered as a possible treatment of his chronic pain, especially in light of the failure of multiple analgesic alternatives. A controlled substance agreement, with follow-up monitoring (aided by the 4 A's[8]) can help the physician monitor the patient for aberrant drug-taking behaviors and, potentially, limit them.

During the course of therapy with oxycodone CR, Gordon escalated his opioid dose in an attempt to relieve his BTP. As a result, he ran out of his prescribed medication early and had to return to the clinician to obtain a refill. This type of aberrant drug-taking behavior can be a symptom of pseudoaddiction, a syndrome that results from undertreatment of pain and should be distinguished from addiction and diversion.[9] Pseudoaddiction can be diagnosed by determining the patient's response to a structured treatment plan that includes

reasonable increments in analgesic doses. When pseudoaddiction is addressed with better analgesic coverage, the aberrant behaviors cease.[10]

Gordon's difficulty in finding the right dose of his opioid medication is not uncommon. Individual patients often differ in the dose required for sufficient analgesia, and patients such as Gordon, who increase their activity, may then require more pain relief. Close follow-up, patience, trust, and clear communication are essential to ensure that treatment outcomes are met and aberrant drug-related behaviors are diagnosed and managed correctly

In Gordon's case, the addition of OTFC, a different opioid with a pharmacokinetic profile matching the temporal characteristics of his incident BTP, proved effective in pre-empting and relieving his debilitating BTP. The ROOs OTFC and FBT are effective as pretreatment for incident pain and as treatment for the unpredictable (idiopathic or spontaneous) type of BTP. They are FDA-approved for use in opioid-tolerant patients with cancer. In a Cochrane Collaboration Review of evidence from 4 studies that included data from 393 participants with cancer, OTFC was superior to placebo, morphine IR, and previous rescue medication (eg, morphine, oxycodone, hydromorphone, and hydrocodone), with a weighted mean difference of –0.68 (95% confidence interval [CI], –1.03 to –0.34) for pain intensity at 15 minutes and –0.91 (95% CI, –1.23 to –0.59) for pain intensity at 30 minutes.[11] The OTFC formulation also was superior in delivering pain relief at 15 minutes (0.54 [0.40-0.69]) and 30 minutes (0.61 [0.47-0.75]). In addition, it showed superior overall global performance compared with previous rescue medication and placebo (0.76 [0.58-0.95]).[11]

Conclusion

CRPS can be a difficult disease to treat In Gordon's case, after numerous other therapies had failed, an LAO (oxycodone CR) proved effective in controlling his baseline persistent pain. However, the physician also had to manage 2 types of BTP. end-of-dose failure, treated by increasing the dose of the long-acting oxycodone (an alternative might have been to shorten the dosing interval), and incident pain, treated with an ROO. When opioids are prescribed, care must be taken to assess the patient's risks for aberrant drug-taking behaviors and then manage them by structuring therapy—including follow-up

appointments—pursuant to the patient's risk profile. A Universal Precautions approach, including controlled substance agreements and UDT, may be useful.[12]

References

1 Schwartzman RJ, Alexander GM, Grothusen J. Pathophysiology of complex regional pain syndrome. *Expert Rev Neurother.* 2006,6(5) 669-681.

2 Stanton-Hicks M. Complex regional pain syndrome manifestations and the role of neurostimulation in its management. *J Pain Symptom Manage.* 2006,31(4 suppl):S20-S24.

3 Stanton-Hicks MD, Burton AW, Bruehl SP, et al. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Pract.* 2002,2(1). 1-16

4. Rowbotham MC. Pharmacologic management of complex regional pain syndrome. *Clin J Pain.* 2006,22(5):425-429

5 Nelson DV, Stacey BR. Interventional therapies in the management of complex regional pain syndrome. *Clin J Pain.* 2006,22(5):438-442.

6. Bennett DS, Brookoff D. Complex regional pain syndromes (reflex sympathetic dystrophy and causalgia) and spinal cord stimulation. *Pain Med.* 2006, 7(S1) S64-S96

7 Gilson AM, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997-2002. *J Pain Symptom Manage.* 2004,28(2):176-188.

8. Passik SD, Weinreb HJ. Managing chronic nonmalignant pain: overcoming obstacles to the use of opioids. *Adv Ther.* 2000;17(2).70-83.

9. Katz NP, Adams EH, Chilcoat H, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain.* 2007;23(8): 648-660.

10 Weaver M, Schnoll S. Abuse liability in opioid therapy for pain treatment in patients with an addiction history. *Clin J Pain.* 2002;18(4 suppl):S61-S69.

11 Zeppetella G, Ribeiro MD. Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database Syst Rev.* 2006; (1):CD004311

12. Fine PG. Risk assessment and management in long-term opioid therapy. In. *The Diagnosis and Treatment of Breakthrough Pain.* New York, NY. Oxford University Press, 2008

Chapter 6: Nancy

A Patient With Diabetic Peripheral Neuropathic Pain

Note: In this case, the patient has been diagnosed with diabetic peripheral neuropathic pain (DPNP). Medically, the editors regard this as the same condition as that described by the terms *neuropathic pain associated with diabetic peripheral neuropathy* and *painful diabetic neuropathy*. In this chapter, the term *DPNP* will be used.

Case

Nancy, a 48-year-old woman with a history of type 2 DM for 10 years, presents to her PCP with sensations of pain and tingling in both feet and ankles. The pain, which is consistently moderate to severe throughout the day, worsens in the evening, with occasional unpredictable spikes that she describes as "unbearable." These exacerbations do not correlate with any obvious activity, nor do they occur at consistent times. The pain was initially limited to her feet, but during the past 6 months, it has worsened and spread to her ankles, sometimes manifesting as a burning sensation, other times as tingling. The pain interferes with her ability to walk, socialize, and sleep.

Nancy describes feeling overwhelmed by ADLs such as child care, cooking, and household chores. In view of her difficulties, her husband has encouraged her to seek further medical evaluation. Initially, she was unwilling, insisting that her problems are a "normal part of having diabetes."

Current Medications

Nancy takes metformin 1,000 mg daily. She has used APAP (1,000 mg 3 times daily) and ibuprofen (400 mg 3 times daily) without benefit.

Medical History

Nancy has been overweight since childhood. When she was given a diagnosis of type 2 DM 10 years earlier, her BMI was 43 kg/m^2 and her hemoglobin A_{1c} value was 6.4%. She was advised to follow an exercise and dietary regimen, but she did not comply and only irregularly attended follow-up appointments with her PCP. She remained

hyperglycemic. Her physician prescribed metformin 5 years ago, which has controlled her hyperglycemia.

Two years before her current visit, Nancy experienced pain in her lower back and was successfully treated by a chiropractor. When Nancy recently expressed hopelessness about her condition, her PCP referred her to a psychiatrist, but she never made an appointment.

Family History

Nancy's mother was obese and had type 2 DM.

Social History

Nancy is married with 2 children, aged 9 and 11. She worked as a secretary before having a family and now intermittently volunteers at her children's schools. Her husband works as an office manager for a construction company. Three months before the current visit, Nancy stopped her volunteer work because of severe pain. She has grown increasingly sedentary since then, spending much of her time at home watching television with her feet up. Her husband reports that her mood has changed over the past year, and that she gets angry at him and their children with little provocation—statements she vehemently denies.

Examination and Diagnosis

Nancy's temperature (98.5°), BP (114/72 mm Hg), HR (71 beats/min), and RR (16 breaths/min) are normal, and her BMI is now 46 kg/m^2. Laboratory studies reveal that Nancy's hemoglobin A_{1c} value is 6.8% and her blood level of thyroid-stimulating hormone is normal. The average daily intensity of her pain is reported as 7/10, with spikes to 9-10/10. The PCP notes other results, including a normal nondilated funduscopic examination, lungs clear to auscultation, a normal cardiac examination, intact peripheral pulses, and good capillary refill. Examination of the liver and spleen is limited by her physique. Nancy is still menstruating. Because the physician is concerned about the potential for sleep apnea, he asks if she snores, measures her neck circumference, and uses the Mallampati score—a visual means of assessing the airway—but finds no abnormalities.

Nancy reports that she inspects her feet several times per month, and no evidence of foot ulcers has been found. The PCP performs

routine sensory testing, examining the most distal aspects of the lower extremities first and then proceeding proximally until the examination normalizes. Nancy reports no vibration sensation at either hallux when she is tested with a 128-Hz tuning fork and demonstrates an increased vibratory threshold to her knees bilaterally. She exhibits tactile allodynia and reduced tactile sensation from her feet to her calves, but also hyperalgesia to pinprick in both feet. Ankle reflexes are absent, but knee jerks and upper extremity deep tendon reflexes are normally active

Given the symmetric pattern of sensation loss and Nancy's medical history, the PCP suspects that Nancy is experiencing signs and symptoms of DPNP. He also notes that Nancy exhibits signs of depression, including self-neglect (unwillingness to comply with exercise and dietary regimens and delays in seeing her physicians), lack of interest in pleasurable activities, feelings of hopelessness, and change in mood.

The PCP administers Nancy the Brief Pain Inventory for Painful Diabetic Peripheral Neuropathy (BPI-DPN), a validated self-assessment questionnaire for patients who have pain associated with DPNP; her scores of greater than 7 on multiple domains, including worst pain, mood, enjoyment of life, and normal work, suggest that the neuropathy is severely interfering with her activities of daily living.

On the basis of the clinical history, examination findings, and neurologic test results, Nancy's physician diagnoses DPNP and major depressive disorder (MDD).

Treatment and Management

The PCP explains to Nancy the importance of maintaining glycemic control and reminds her that currently available treatments make it possible for patients to exercise a certain degree of control over DM, so she need not feel helpless. He emphasizes the importance of regular foot care and medical follow-up and again urges her to see the psychiatrist.

The physician prescribes duloxetine at a starting dose of 30 mg daily, which is increased after 1 week to 60 mg daily. This is done to minimize the occurrence of adverse effects such as nausea. At a 1-month follow-up appointment, Nancy reports a decrease in the level of her daily pain to 1-3/10, in addition to an improved ability to perform ADLs. Furthermore, she reports feeling happier and less anxious. Her

husband corroborates the improvement in her mood

Despite the improvement in her baseline pain control, Nancy reports unpredictable flares of pain that reach an intensity of 7-9/10 and occur 3 to 4 times weekly. Her duloxetine dose is increased to 60 mg twice daily. The increased daily duloxetine is not effective for this idiopathic BTP. The physician has a discussion with Nancy about the risks and benefits of opioid therapy and assesses her risk for opioid misuse with the SOAPP-R, on which she scores an 8, indicating low risk. The PCP then prescribes oxycodone 5 mg/APAP 325 mg, to be taken immediately when she feels the onset of a painful episode. Nancy finds that the medication, when combined with rest, helps alleviate her BTP. She occasionally takes a second dose 4 to 6 hours later if the pain does not subside.

Although Nancy's mood has improved, she sometimes still feels depressed. Nancy agrees to see the psychiatrist biweekly and to follow up with her PCP every 3 months.

Discussion

DPNP occurs in approximately 16% to 26% of the diabetic population.[1] This is an estimate, however, because available studies have used different measures and criteria for diagnosing neuropathy, and the condition may often be asymptomatic. Furthermore, painful neuropathy can occur in patients with impaired glucose tolerance but not frank DM.[2]

The course faced by patients with DPNP is challenging.[3] In addition to pain, they may have complications such as diabetic foot ulcers, tissue devascularization, cardiovascular disease, and MDD.[4,5] The impact of DPNP on QoL and health care utilization costs is significant. Neuropathy, whether diabetic or from another origin, is associated with 87% of the approximately 85,000 amputations performed in the United States each year.[6] Compared with diabetic patients who do not have neuropathy, a patient such as Nancy incurs higher medical costs,[7] experiences a greater reduction in QoL,[8] and is 1.7 times more likely to require an amputation.[6]

The diagnosis and management of DPNP can be achieved on the basis of the patient's history and a thorough physical examination. Because DPNP is asymptomatic in up to 50% of patients and because pain symptoms tend to be underreported, assessment for neuropathy

is crucial in patients with DM (Table 1).[9] A careful examination of foot sensitivity requires tests of pressure, temperature, vibration, pain, and light and sharp touch. Ankle reflexes are often absent in patients with DPNP; however, the presence of ankle reflexes does not by itself rule out DPNP.[9] In patients presenting with pain, a validated questionnaire, such as the Neuropathic Pain Questionnaire, BPI-DPN, or Michigan Neuropathy Screening Instrument, provides insights into the patient's pain experience.[9]

During the examination, it is important to consider and rule out other causes of pain, such as HIV infection, metastatic disease, postherpetic neuralgia, and osteoarthritis.[9] Some pain descriptors may suggest the presence of DPNP in a patient with DM, such as an affirmative answer to the question, "Do your feet burn, hurt, or tingle?" Although multiple types of DPNP exist, the most common presentation, as seen in this patient, is a symmetric distribution of pain beginning in the distal extremities and spreading proximally.[9] In addition, the presence of comorbidities such as diabetic retinopathy, nephropathy, depression, sleep disturbances, muscle weakness, and foot ulcers may suggest a diagnosis of DPNP when appropriate symptoms are present. Patients with DPNP may experience other complications of DM, including increased risk for cardiovascular disease and cerebrovascular disease.[10] Finally, 2 simple neurologic testing tools have been validated for diagnosing diabetic neuropathy: application of the 10-g Semmes-Weinstein monofilament to the plantar surface of the foot and application of a 128-Hz tuning fork to the apex of the big toe to check for the intensity threshold of vibration sensation.[9,11]

Nancy's weight is a risk factor for sleep apnea, and although she did not have that disorder (as established by neck circumference, Mallampati score, and lack of snoring), it is important to assess for sleep disorders in patients with obesity. In addition, a recent study showed a high prevalence of sleep-disordered breathing (75%) in patients with chronic pain who were treated with opioids, with a significant association observed between methadone use and sleep apnea.[12] Opioids are known to disturb sleep architecture, the pattern of stages needed for restorative sleep.[13]

Although there is no cure for DPNP, effective treatment of hyperglycemia may delay its onset,[14-16] and effective pain management

Table 1. Key Elements in the Diagnosis of Diabetic Peripheral Neuropathic Pain[7]

Establish diagnosis of DM or IGT.

Diagnostic values are 2-hour OGTT >200 mg/dL for diabetes and 140-199 mg/dL for IGT.

Establish presence of neuropathy.

Use validated questionnaires (NPQ, BPI-DPN, MNSI).

Use simple, handheld screening devices (10-g monofilament, 128-Hz tuning fork).

Assess pain characteristics:

- distal, symmetric
- numbness; tingling vs burning, aching, throbbing pain
- spontaneous (continuous or intermittent) vs stimulus-evoked pain

Rule out nondiabetic causes for neuropathy and/or pain:

- metastatic disease
- infection
- toxic substances

BPI-DPN, Brief Pain Inventory for Diabetic Peripheral Neuropathy, **DM,** diabetes mellitus; **IGT,** impaired glucose tolerance, **MNSI,** Michigan Neuropathy Screening Instrument, **NPQ,** Neuropathic Pain Questionnaire, **OGTT,** oral glucose tolerance test

may help avoid disability and related impairments. Evidence-based guidelines have been written for the treatment of DPNP[9] and neuropathic pain in general.[17] Based on randomized, controlled trials and clinical experience, tricyclic antidepressants (TCAs) such as amitriptyline, desipramine, and nortriptyline are effective in DPNP.[18,23] Although TCAs have the advantage of being inexpensive, adverse events limit their utility in some patients. The most common risk factors are cardiovascular disorders, cardiac arrhythmias, and the use of thyroid medication.[22] SNRIs are associated with fewer adverse events than TCAs, however, they are more expensive and contraindicated in patients already taking monoamine oxidase inhibitors.[3] The SNRI venlafaxine has shown evidence of efficacy in randomized, controlled trials compared with placebo[24] and imipramine.[25]

Two agents are FDA-approved for the treatment of DPNP: the SNRI duloxetine[26-28] and the $\alpha_2\delta$ ligand pregabalin.[29-31] In Nancy's case, duloxetine seems a promising choice because, in addition to her pain, it may help to treat her depression. Evidence of efficacy also is available for the $\alpha_2\delta$ ligand gabapentin[19,32] and 2 older anticonvulsants, carbamazepine and lamotrigine,[22,33,34] although the evidence of efficacy for lamotrigine in various neuropathic pain states is mixed.[34-36]

Differing recommendations are offered in recent review articles comparing the effectiveness of duloxetine and pregabalin with that of older drug classes. A review by Wong et al[37] concludes that TCAs and traditional anticonvulsants should both precede oxycodone, duloxetine, or pregabalin in the treatment algorithm, the latter were regarded as among the first-tier agents by Argoff et al [3] However, work by Sindrup et al[38] points out flaws in the study of Wong et al[37] that may have led these investigators to overestimate the effectiveness of traditional anticonvulsants and downplay the effectiveness of drugs such as pregabalin and duloxetine. Based on the quality of evidence and on evidence of efficacy and safety, Moulin et al[39] and Finnerup et al[40] conclude that TCAs and $\alpha_2\delta$ ligand anticonvulsants deserve first-tier status, whereas SNRIs more generally deserve second-tier status (the guidelines from Moulin et al were developed in Canada, where duloxetine was not available at the time).

Tramadol—a medication that blocks the reuptake of serotonin and norepinephrine and whose metabolite acts as a weak opioid agonist—and oxycodone CR have both shown efficacy in treating DPNP.[41-44] If the decision is made to institute a trial of opioid therapy as a component of pain management for DPNP, it is important that the clinician perform a risk assessment, structure treatment accordingly, and monitor for typical opioid-related adverse effects.[45] As in Nancy's case, opioids may play an important role in the management of BTP in DPNP when used in combination with pain-modifying drugs from different pharmacologic classes, according to the principles of rational multidrug therapy. This may produce better analgesia, at lower doses and with fewer side effects, than any of the drugs used alone.

In addition to systemic therapies, topical treatments may be useful. Creams containing capsaicin provide effective analgesia in patients with pain who can tolerate the initial increase in burning pain that

the treatment may cause [46] The 5% lidocaine patch is another topical treatment for pain with few adverse effects and evidence of efficacy in DPNP based on the results of an open-label study.[47]

Conclusion

The management of DPNP remains challenging. Common comorbidities, such as cardiovascular disease, mood disturbance, and sleep apnea, must be assessed and treated as part of a comprehensive therapeutic plan.[16] When used with due caution and ongoing monitoring for therapeutic and adverse effects, pharmacotherapy can be a very helpful approach to reducing the pain, distress, and debility associated with DPNP

References

1 Jensen TS, Backonja MM, Jiménez SH, Tesfaye S, Valensi P, Ziegler D. New perspectives on the management of diabetic peripheral neuropathic pain *Diabetes Vasc Dis Res* 2006;3(2) 108-119

2 Singleton JR, Smith AG, Bromberg MB. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care*. 2001;24(8):1448-1453.

3 Argoff CE, Backonja MM, Belgrade MJ, et al Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain. *Mayo Clin Proc*. 2006,81(suppl 4):12-25.

4 Sumpio BE Foot ulcers. *N Engl J Med* 2000,343(11).787-793.

5. Grundy SM, Benjamin IJ, Burke GL, et al Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association *Circulation*. 1999;100(10).1134-1146.

6. Vinik AI, Mehrabyan A. Diabetic neuropathies *Med Clin North Am*. 2004; 88(4):947-999.

7. Le TK, Able SL, Lage MJ. Resource use among patients with diabetes, diabetic neuropathy, or diabetes with depression *Cost Eff Resour Alloc* 2006 Oct 23;4:18

8. Vinik EJ, Hayes RP, Oglesby A, et al. The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. *Diabetes Technol Ther*. 2005;7(3). 497-508

9 Argoff CE, Cole BE, Fishbain DA, Irving GA Diabetic peripheral neuropathic pain clinical and quality-of-life issues *Mayo Clin Proc*. 2006,81(suppl 4): 3-11.

10 Retnakaran R, Zinman B. Type 1 diabetes, hyperglycaemia, and the heart. *Lancet*. 2008;371·1790-1799

11 Boulton AJM, Arezzo JC, Malik RA, Sosenko JM. Diabetic somatic neuropathies. *Diabetes Care*. 2004;27(6):1458-1486.

12. Webster LR, Choi Y, Desai H, Webster L, Grant BJB. Sleep-disordered breathing and chronic opioid therapy. Online Early Articles. doi.10.1111/j.1526-4637.2007.00343.x.

13 Dimsdale JE, Norman D, DeJardin D, Wallace MS. The effect of opioids on sleep architecture. *J Clin Sleep Med*. 2007;3(1):33-36.

14. Boulton AJM, Freeman R, Vinik AI, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care*. 2005;28(4):956-962.

15 Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1995;333(2):89-94.

16 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986.

17. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132(3):237-251 [published online ahead of print October 24, 2007].

18 Max NB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology*. 1987;37(4):589-596.

19. Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med*. 1999;159(16):1931-1937.

20 Max MB, Kishore-Kumar R, Schafer SC, et al. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. *Pain*. 1991;45(1):3-9.

21 Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med*. 1992;326(19):1250-1256.

22. Gómez-Pérez FJ, Choza R, Ríos JM, et al. Nortriptyline-fluphenazine versus carbamazepine in the symptomatic treatment of diabetic neuropathy. *Diabetes Res Clin Pract*. 1996;27(4):525-529.

23. Berger A, Dukes E, Hagiwara M, Edelsberg J, Stacey B, Oster G. Lewin Group Analysis Incorporated. Use of tricyclic antidepressants in painful diabetic peripheral neuropathy. *J Pain*. 2005;6(suppl 1):35 D03-a-d.

24 Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain*. 2004;110(3):697-706.

25. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. *Neurology*. 2003;60(8):1284-1289.

26 Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S Duloxetine vs placebo in patients with painful diabetic neuropathy. *Pain* 2005;116(1-2).109-118

27 Raskin J, Pritchett YL, Wang F, et al A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain *Pain Med* 2005,6(5) 346-356

28 Wernicke JF, Pritchett YL, D'Souza DN, et al A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain *Neurology* 2006;67(8) 1411-1420.

29. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy a randomized controlled trial *Neurology*. 2004, 63(11) 2104-2110

30 Richter RW, Portenoy R, Sharma U, Lamoreaux L, Bockbrader H, Knapp LE Relief of painful diabetic peripheral neuropathy with pregabalin a randomized, placebo-controlled trial *J Pain*. 2005;6(4) 253-260

31 Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy a double-blind, placebo-controlled trial *Pain* 2004,110(3) 628-638.

32 Backonja M, Beydoun A, Edwards KR, et al Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus a randomized controlled trial. *JAMA*. 1998,280(21)·1831-1836

33 Wilton TD Tegretol in the treatment of diabetic neuropathy *S Afr Med J* 1975,48(20)·869-872

34. Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A Lamotrigine reduces painful diabetic neuropathy. a randomized, controlled study *Neurology*. 2001;57(3):505-509.

35. Simpson DM, McArthur JC, Olney R, et al, Lamotrigine HIV Neuropathy Study Team Lamotrigine for HIV-associated painful sensory neuropathies. a placebo-controlled trial *Neurology* 2003;60(9)·1508-1514

36. Simpson DM, Olney R, McArthur JC, Khan A, Godbold J, Ebel-Frommer K. A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy *Neurology*. 2000;54(11).2115-2119.

37. Wong MC, Chung JW, Wong TK Effects of treatments for symptoms of painful diabetic neuropathy. systematic review. *BMJ*. 2007;335(7610). 87-96.

38 Sindrup SH, Tesfaye S, Otto M, Bach FW. Systematic review on treatments for painful diabetic neuropathy skips important studies and accepts dubious findings in others leading to an invalid treatment algorithm. *BMJ* Web site http://www.bmj com/cgi/eletters/335/7610/87. Accessed October 30, 2007

39 Moulin DE, Clark AJ, Gilron I, et al Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag*. 2007;12(1).13-21

40 Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH Algorithm for neuropathic pain treatment: an evidence-based proposal *Pain* 2005;118(3) 289-305.

41. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology*. 2003; 60(6):927-934.

42. Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain*. 2003;105(1-2):71-78.

43. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology*. 1998; 50(6):1842-1846.

44. Sindrup SH, Andersen G, Madsen C, Smith T, Brøsen K, Jensen TS. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. *Pain*. 1999;83(1):85-90.

45. Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. 2nd ed. New York, NY: Vendome Press; 2008.

46. Capsaicin Study Group. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. *Diabetes Care*. 1992;15(2): 159-165.

47. Barbano RL, Herrmann DN, Hart-Gouleau S, Pennella-Vaughan J, Lodewick PA, Dworkin RH. Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. *Arch Neurol*. 2004;61(6): 914-918.

Chapter 7: Marie

A Patient With Osteoporosis

Case

Marie, a 58-year-old woman, presents to her PCP 5 days after experiencing the sudden onset of severe back pain while attempting to open a window. She describes her pain as varying in intensity throughout the day, increasing with activity and abating somewhat when she lies down. The pain is most severe over her lower back, and it does not radiate.

Current Medications

Marie's current medications include 40 mg of simvastatin daily for dyslipidemia and 180 mg of fexofenadine nightly for perennial rhinitis. She has taken APAP (1,000 mg 3 or 4 times daily), which has not relieved her pain. She also takes a multivitamin with minerals and a chewable calcium and vitamin D supplement 3 times daily for a total of 1,500 mg of calcium and 400 IU of vitamin D per day.

Medical History

Marie's medical history is significant only for dyslipidemia and perennial rhinitis with seasonal exacerbations. Menopause occurred at age 52; she does not take supplemental hormones. Her 2 pregnancies were uneventful and the deliveries normal. She has never smoked and reports drinking an average of 3 glasses of red wine per week.

Family History

Marie's mother and maternal grandmother had osteoporosis.

Social History

Marie is married, has a grown son and daughter, maintains an active lifestyle, and enjoys hiking with her husband. She works full-time as a tax accountant.

Examination and Diagnosis

Vital signs include BP, 117/74 mm Hg; HR, 65 beats/min; RR, 15 breaths/min; temperature, 98.4°F; pain intensity score, 9/10. A

focused physical examination reveals a woman of slight build who is in obvious distress. Lower back flexion and extension are limited because of severe pain. Side-to-side motion also elicits severe pain in her lower back. Even at rest, marked tenderness is noted over the upper lumbar vertebrae. Results of her neurologic examination are normal.

Bone mineral density (BMD) testing reveals a T-score of –3.8 SD at the lumbar spine. This value is sufficient for a diagnosis of osteoporosis, based on WHO guidelines defining osteoporosis as a T-score of –2.5 SD or lower, and severe osteoporosis as a T-score of –2.5 SD or lower with 1 or more fragility fractures. Laboratory tests indicate that her serum levels of calcium, phosphorus, vitamin D_3, 25-hydroxyvitamin D_3, and vitamin D_2 all are within normal limits.

Treatment and Management

Marie's PCP advises her to continue the calcium and vitamin D supplementation and prescribes 70 mg of the bisphosphonate alendronate weekly to treat her osteoporosis, along with 200 IU of intranasal salmon calcitonin daily. He recommends 200 mg of ibuprofen 4 times daily

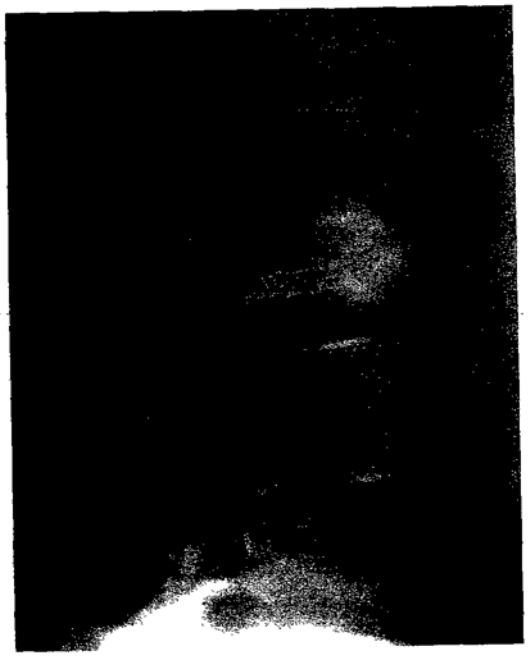


Figure 1. X-ray showing osteoporotic compression fracture in Marie's L2 vertebra.

for ATC pain relief and prescribes 50 mg of tramadol IR 4 times daily as needed for severe pain.

After 6 weeks on this regimen, Marie's condition does not improve, and X-ray and MRI examinations of her lumbar spine reveal a subacute osteoporotic compression fracture of the second lumbar (L2) vertebra (Figure 1), amending her diagnosis to severe osteoporosis She is referred to an orthopedic surgeon for a kyphoplasty procedure, which is performed the next day. She is then referred for physical therapy to enhance her mobility and help prevent further fractures.

During the next week, Marie's pain escalates and is punctuated by bursts of still more severe pain when she lifts light objects, leans or bends slightly, or missteps while walking. The orthopedist tells her that the effects of the kyphoplasty should have been maximized by now. By the end of the next week, her pain remains severe, at 9/10, interfering with her ADLs, including sleep

Marie schedules an urgent appointment with her PCP because of uncontrolled pain. He notes significant negative changes in Marie's demeanor; she described herself as in good health at her first presentation, but at each subsequent visit she indicates an increasingly poor perception of her well-being. When the PCP discusses this with Marie, she admits that the constant pain is having a negative effect on all aspects of her life.

The PCP tells Marie that it is not unusual to obtain only partial relief from surgical procedures such as kyphoplasty, and that she may be able to achieve better analgesia and functionality with opioid therapy. She resists, noting that she does not want to "take narcotics for the rest of my life." Her comment leads to a conversation about the potential effectiveness of opioids, during which she reveals concerns about side effects and drug addiction. The terms *tolerance*, *physical dependence*, and *addiction* are discussed with her and defined. The PCP explains that addiction is a disease characterized by craving and impaired control over drug use (Chapter 1), tolerance is the state of adaptation in which exposure to a drug results in diminution of one or more of the drug's effects over time, and physical dependence is the state of adaptation manifested by a withdrawal syndrome that can be produced by abrupt drug cessation. Marie understands that although she is likely to become physically dependent, she will be able to discontinue the drug without withdrawal symptoms, as long as the dose

is tapered and the drug is not stopped abruptly.

Marie eventually agrees to a trial of opioid therapy, tramadol is tapered over 2 weeks, and SAO treatment is initiated with hydrocodone 5 mg/APAP 500 mg 4 times daily. This agent immediately relieves her pain and makes it possible to establish an effective analgesic dose. Marie, however, reports that severe pain breaks through at the end of each dosing interval, so her medication is switched to a once-daily LAO, 30 mg of morphine sulfate ER.

The LAO adequately relieves Marie's persistent baseline pain as well as the pain associated with end-of-dose failure, but it causes nausea and constipation, which resolve with medical management (25 mg of hydroxyzine 4 times daily for the nausea and 2 mg of senna concentrate at bedtime for the constipation) and a high-fiber diet. Marie describes improved sleep and functionality, indicating that she has resumed most of her usual activities.

Discussion

Osteoporosis is characterized by a reduction in bone mass, deterioration of bone microarchitecture, loss of bone strength, and an increased risk for fracture. It is often defined in clinical terms by a low BMD. The National Osteoporosis Foundation estimates that 20% of postmenopausal white women in the United States have osteoporosis and that an additional 52% have osteopenia (low bone mass, defined as a T-score between –1 SD and –2.5 SD) at the hip. This amounts to 7.8 million women with osteoporosis and an additional 21.8 million with osteopenia at the hip. It is also estimated that 50% of all white women will experience an osteoporotic fracture at some time during their life.[1]

Vertebral fractures can be difficult to identify on a clinical basis alone.[2] In Marie's case, however, the index of suspicion is high. She has known risk factors for osteoporosis—female gender, postmenopausal status, slight build, family history of osteoporosis, and white race.[3] The onset of her severe back pain was associated with a clearly identified activity, and her pain was localized and persistent. X-ray films later revealed a compression fracture of the L2 vertebra.

BMD testing should be conducted to confirm the diagnosis and determine the severity of disease.[1] Malignancy should be considered and ruled out as the cause of the fracture. Treatable causes of secondary

Table 1. Medical Conditions That May Be Associated With Increased Risk for Osteoporosis[1]

AIDS/HIV infection
Amyloidosis
Ankylosing spondylitis
Chronic obstructive pulmonary disease
Congenital porphyria
Cushing's syndrome
Eating disorders (eg, anorexia nervosa)
Gastrectomy
Gaucher's disease
Hemochromatosis
Hemophilia
Hyperparathyroidism
Hypogonadism, primary and secondary (eg, amenorrhea)
Hypophosphatasia
Idiopathic scoliosis
Inadequate diet
Inflammatory bowel disease
Insulin-dependent diabetes mellitus
Lymphoma and leukemia
Malabsorption syndromes
Mastocytosis
Multiple myeloma
Multiple sclerosis
Pernicious anemia
Rheumatoid arthritis
Severe liver disease, especially primary biliary cirrhosis
Spinal cord transsection
Sprue
Stroke (cerebrovascular accident)
Thalassemia
Thyrotoxicosis
Tumor secretion of parathyroid hormone–related peptide
Weight loss

osteoporosis can be identified or ruled out through a biochemical evaluation of serum and urine samples (Table 1, page 79).[1,2]

There is no consensus on the optimal management of an acute painful vertebral fracture related to osteoporosis, although various measures have been recommended (Figure 2).[4] After diagnosis and investigation for any underlying cause, NSAIDs can be used for analgesia, with bed rest minimized. Thereafter, 200 IU of calcitonin daily for 14 days and/or opioid analgesia can be prescribed.[4-6] If severe pain persists after 6 weeks, MRI should be performed, and vertebroplasty or kyphoplasty can be considered.[4,7] In Marie's case, the severity of her pain prompted her PCP to refer her to an orthopedist for a procedure; unfortunately, the procedure was not successful.

Marie's observation that her health and well-being were deteriorating is in keeping with the results of a detailed study of the epidemiology of pain and health-related QoL in 150 consecutive patients with chronic nonmalignant pain who were managed at a multidisciplinary pain center. In that study, patients with chronic noncancer pain had poorer health-related QoL than patients with many other medical conditions, a finding that underscores the need for adequate pain management in all patients.[8]

Pain management must be tailored to individual needs through a consideration of pharmacologic,[9] nonpharmacologic,[10] interventional,[10-12] and surgical options, with the goal of maintaining physical, emotional, and social function.[13] Marie's experience with once-daily morphine sulfate ER is consistent with the results of clinical studies showing the efficacy of such treatment in relieving moderate to severe back pain and improving function and sleep.

Conclusion

Although often silent, osteoporotic vertebral fractures can be associated with severe pain and significant morbidity. Individuals who present with the sudden onset of severe back pain and have risk factors for osteoporosis should be evaluated for vertebral fracture, and an underlying cause should be sought. Bed rest should be minimized if possible, and the pain should be managed in a stepwise fashion with NSAIDs, salmon calcitonin, and opioids if necessary. Patients with severe back pain that persists for longer than 6 weeks should undergo MRI, with vertebroplasty or kyphoplasty considered if appropriate.

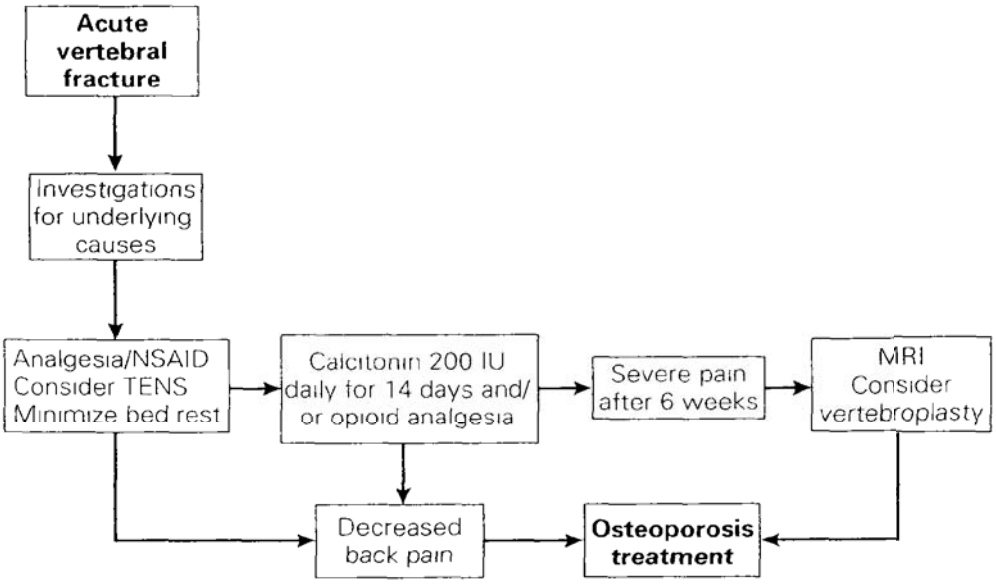


Figure 2. Schematic representation of the acute management of a symptomatic vertebral fracture.[4]

MRI, magnetic resonance imaging, **NSAID**, nonsteroidal anti-inflammatory drug, **TENS**, transcutaneous electrical nerve stimulation

Marie did not experience complete relief of pain following surgery, but she was able to control her pain later with an NSAID and an LAO.

References

1. National Osteoporosis Foundation. *Physician's Guide to Prevention and Treatment of Osteoporosis*. Washington, DC: National Osteoporosis Foundation; 2003.

2. Lenchik L, Rogers LF, Delmas PD, Genant HK. Diagnosis of osteoporotic vertebral fractures: importance of recognition and description by radiologists. *AJR Am J Roentgenol* 2004,183(4):949-958.

3 National Institutes of Health. Osteoporosis overview. http://www.niams.nih gov/Health_Info/Bone/Osteoporosis/default.asp Accessed January 3, 2008

4. Francis RM, Baillie SP, Chuck AJ, et al. Acute and long-term management of patients with vertebral fractures *QJM*. 2004;97(2):63-74.

5. Knopp JA, Diner BM, Blitz M, Lyritis GP, Rowe BH. Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials *Osteoporos Int*. 2005;16(10): 1281-1290.

6 McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther* 2001;8(3):181-186.

7 Lavelle W, Carl A, Lavelle ED, Khaleel MA. Vertebroplasty and kyphoplasty. *Anesthesiol Clin* 2007;25(4):913-928.

8 Becker N, Bondegaard Thomsen A, Olsen AK, et al. Pain epidemiology and health-related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. *Pain* 1997;73(3):393-400.

9 Argoff CE. Pharmacotherapeutic options in pain management. *Geriatrics* 2005 Nov;suppl:3-9.

10 Grabois M. Management of chronic low back pain. *Am J Phys Med Rehabil* 2005;84(3 suppl):S29-S41.

11. Manchikanti L, Singh V, Bakhit CE, Fellows B. Interventional techniques in the management of chronic pain: part 1.0. *Pain Physician*. 2000;3(1):7-42.

12. Manchikanti L, Singh V, Kloth D, et al. Interventional techniques in the management of chronic pain: part 2.0. *Pain Physician*. 2001;4(1):24-96.

13 Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. *Neurology* 2007; 68(15):1178-1182.

Chapter 8: Abraham

A Patient With Chemotherapy-Induced Neuropathic Pain

Case

Abraham, a 58-year-old man with a history of stage IV prostate cancer, is referred to a neurologist because of the recent onset of sharp, shooting pain, tingling, and numbness in both thighs and distal lower extremities. Abraham complains of difficulty walking due to stiffness in both lower extremities. His oncologist has noted significant hyperreflexia and increased muscle tone (spasticity) in both lower extremities. Abraham and his family are fearful that the cancer has returned.

Ten years ago, Abraham underwent a radical prostatectomy for the treatment of stage I prostate cancer. His oncologist followed him annually for several years, monitoring his prostate-specific antigen (PSA) levels. Three years ago, Abraham presented to his PCP with severe midthoracic spinal pain. It was subsequently determined that his prostate cancer had metastasized to the epidural region between the T6 and T8 thoracic vertebrae, causing epidural spinal cord compression at T7 and T8. At that time, Abraham underwent treatment for stage IV prostate cancer: surgery followed by external-beam radiation to the spine, chemotherapy (docetaxel), and intermittent hormonal therapy with leuprolide, in addition to oxycodone/APAP for pain. He has been stable for more than 2 years and is currently under the care of a urologist and an oncologist.

Current Medications

Abraham currently is not taking any medications.

Medical History

Abraham has no history of medical illness other than prostate cancer. His surgical history is notable for an appendectomy at age 26. He has no known medical allergies. Abraham has had no recent fever, weight gain, or weight loss. He has had no recent onset of headache, neck pain, or abdominal pain. There has been no recent change in his bowel or bladder function.

Family History

Abraham's family history is negative for psychiatric illness and chemical dependency and is otherwise noncontributory

Social History

Abraham is married with 2 grown sons. He does not smoke and rarely drinks alcohol He is a high school music teacher and plays guitar in a wedding band on the weekends.

Examination and Diagnosis

Based on Abraham's previous medical history, age, and clinical presentation, it is necessary to determine whether his current complaints are related to cancer or noncancerous causes.

Physical examination reveals that Abraham is afebrile; his BP is 110/68 mm Hg; HR, 72 beats/min; and RR, 16 breaths/min. His current pain level is reported as 7/10. His lungs are clear to auscultation Cardiac examination demonstrates normal S_1 and S_2 only, and the abdominal examination finding is benign. Pain is elicited by percussion of his midthoracic spine, but there is no tenderness in his head or neck and no Lhermitte's sign (see discussion). Straight leg raising is negative in the sitting position. The extremities are without cyanosis, clubbing, or edema.

Neurologic examination demonstrates that Abraham is alert and fully oriented. Higher cortical functions are intact. Cranial nerve examination is unremarkable. Motor examination demonstrates that Abraham has a spastic gait with grade 2 spasticity in both lower extremities as measured on the Ashworth Scale (Table 1).[1] He has full strength and normal upper extremity tone and function. Sensory examination reveals intact sensation to pinprick, impaired position sense in the lower extremities, and normal cortical modalities. His deep tendon reflexes are very brisk in both lower extremities but normal in the upper extremities S tained ankle clonus and Babinski's responses are noted bilaterally

Abraham is referred for MRI with contrast of his brain and cervical and thoracic spine as well as a bone scan. Postsurgical changes are noted on the MRI of the thoracic spine, but there is no evidence of metastatic bone disease or new spinal cord or nerve root compression. Electromyography and nerve conduction velocity studies of both lower extremities are unremarkable. Measures of PSA, vitamin

Table 1. Modified Ashworth Scale[1]

0	No increase in tone
1	Slight increase in muscle tone, manifested by a catch and release or minimal resistance at the end of the ROM when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

ROM, range of motion.

rapid plasma reagin, trifluorothymidine, and Lyme titers are all normal.

Following the completion of a detailed physical examination and diagnostic studies, the neurologist and oncologist conclude that no evidence of cancer recurrence, sensorimotor neuropathy, or discogenic abnormalities explains Abraham's symptoms. Because other possible causes have been excluded, the doctors diagnose radiation-induced myelopathy. They assure Abraham and his family that the cancer has not returned.

Treatment and Management

Abraham is prescribed corticosteroids and referred to a physical therapist for evaluation and treatment of his gait problems. The neurologist sequentially prescribes nortriptyline, gabapentin, and tramadol, which fail to provide meaningful pain relief, even at relatively high doses. Abraham is then prescribed pregabalin titrated to 100 mg 3 times daily. His baseline persistent pain is reduced from 7/10 to 6/10, and several times per day he experiences severe, unpredictable flares of pain rated 9/10. He sometimes experiences these episodes when walking. It is suggested that Abraham might benefit from opioid therapy in addition to the pregabalin.

Abraham scores 1 on the ORT, which places him at low risk for the development of aberrant drug-related behaviors. The neurologist documents this in Abraham's chart. The patient has experience with opioid medications (oxycodone) from his prior postsurgical recovery, so the neurologist discusses the expectations of treatment and instructs Abraham to call the office if he experiences suboptimal analgesia rather than to self-escalate the dose. Abraham also is told to fill all prescriptions at the same pharmacy and to keep his medications in a safe place. In addition to the pregabalin, the neurologist prescribes oxycodone 5 mg/APAP 325 mg up to 4 times daily for the idiopathic BTP. The new medication lessens the intensity of his BTP only slightly and requires more than 30 minutes to take effect. His baseline pain also is slightly reduced to 5/10. The neurologist then prescribes oxycodone ER, titrated up to 20 mg twice daily, and tells Abraham he can still take the short-acting medication when he experiences BTP. The new regimen reduces Abraham's baseline level of pain to 3/10 but still does not alleviate his BTP.

Abraham remembers the agreement he made with the neurologist and phones to report these flares of pain. He also notes that the unpredictability of most of his episodes causes him to feel anxious about leaving the house because he is afraid the pain will strike while he is out in public. He is no longer able to play with his band.

The neurologist re-evaluates Abraham and discusses the benefits and risks of switching him to a more rapid-acting and potent medication to alleviate his BTP. He discontinues the oxycodone/APAP and prescribes FBT 100 mcg. After inducing a BTP episode by having Abraham walk up and down the hallway vigorously, he administers the first dose and evaluates the effects. FBT shows good efficacy with no adverse effects. Abraham is told to use this dose up to 4 times daily immediately when he feels the onset of an episode of BTP, but to let at least 4 hours elapse between doses. FBT reliably reduces the intensity of his BTP to a manageable 4-5/10

Discussion

Metastatic spinal cord compression occurs in about 10% of all patients with cancer during the course of their disease.[2] Surgery and radiation therapy often are used to limit the progression of motor deficits due to metastatic spinal cord compression.[3] The life expectancy

of patients with metastatic spinal cord compression can be as little as a few months, depending on the type of tumor. However, patients with prostate cancer in whom metastatic spinal cord compression develops have a relatively good prognosis.[4] As a result, these patients live longer but often experience a recurrence of metastatic spinal cord compression. Surgery is usually restricted to patients with 1 involved vertebra and as a result is not indicated in most cases at this stage.[2,4] With additional radiation the only other treatment available, radiation-induced myelopathy becomes a significant concern (Figure 1).[4]

Cases of radiation myelopathy are of 2 types: early delayed radiation myelopathy and delayed radiation myelopathy.[5] Early delayed radiation myelopathy is a transient condition that occurs 6 weeks to 6 months following radiation therapy. Improvement can be seen within 2 to 9 months, although the condition may persist. Clinical symptoms of early delayed radiation myelopathy are limited to Lhermitte's sign, which consists of short and unpleasant sensations of numbness, tingling, and electricity-like discharge radiating from the neck through the spine to the extremities. Usually, they are triggered by neck flexion. On MRI, the affected area looks normal in most cases.

Delayed, or progressive, radiation myelopathy appears 6 months to 10 years after radiation treatment. Risk factors for this condition include older age, previous irradiation (particularly in childhood), a large

Figure 1. Radiation myelopathy at the level of the sixth cervical vertebra in a 51-year-old man with laryngeal cancer about 11 months after the last irradiation treatment.

area of irradiation, and large radiation doses and fractions. The administration of radiation in combination with chemotherapy also may be a risk factor. MRI may not reveal anything unusual at the onset. However, over time, studies show spinal cord swelling with hypointensity on T1-weighted images and hyperintensity on T2-weighted images. MRI with gadolinium enhancement reveals the condition in approximately 50% of cases.

The pathogenesis of delayed radiation myelopathy is not fully understood; the condition may be the result of demyelination, focal necrosis and axonal loss, or vascular abnormalities.[6] Patients with delayed radiation myelopathy have been treated with corticosteroids, hyperbaric oxygen, and anticoagulants (eg, heparin) with limited success.[5,7-9]

Although therapies for radiation myelopathy are limited, associated myelopathic pain can be treated with multiple modalities, both nonpharmacologic and pharmacologic [10] Myelopathic pain is considered a form of central neuropathic pain and should be treated as such. Several guidelines have been published for the treatment of neuropathic pain.[11-13] Pharmacologic treatments include TCAs (eg, nortriptyline), SNRIs (eg, venlafaxine, duloxetine), sodium channel modulators (eg, lamotrigine, lidocaine), tramadol, and opioids (eg, oxycodone, morphine). Opioids have been recommended as first-line therapy for neuropathic pain.[11,13] A crossover study of TCAs, opioids (methadone and morphine ER), and placebo in post-herpetic neuralgia revealed that opioids provide better relief with minimal side effects.[14]

In Abraham's case, nortriptyline, gabapentin, and tramadol all failed to produce meaningful pain relief, so the physician decided to try opioids. Because opioids are associated with abuse liability, precautions must be taken with all patients before therapy is initiated. Although Abraham had been successfully treated with oxycodone in the recent past, his physician used a validated opioid risk screening tool and documented the result. His score suggested low risk for misuse, and Abraham adhered to the regimen, following his prescriber's recommendations without displaying aberrant behaviors.

The combination of pregabalin with oxycodone/APAP and oxycodone ER effectively reduced Abraham's daily pain level. The flares of severe, unpredictable pain that he still experienced, despite his relatively well-controlled baseline persistent pain, are characteristic of idiopathic BTP and may respond to opioid treatment. The short-acting

oxycodone/APAP did not provide optimal analgesia for Abraham's BTP. When an opioid trial is initiated, it is important for the physician and patient to discuss the expectations and parameters of a successful trial and the conditions of a failed trial, which can result from intolerable adverse effects, inadequate pain control, or aberrant drug-related behavior leading to noncompliance with the treatment plan. Next steps include a change in dosing, rotation to a different agent, augmentation with an agent of a different drug class, or the initiation of interventional or nonpharmacologic treatment. In this case, the patient was successfully rotated to a different agent, FBT, with pharmacokinetic and pharmacodynamic characteristics that better matched the profile of his BTP.

In a randomized, placebo-controlled study of 75 patients who had BTP associated with chronic noncancer neuropathic pain, FBT showed efficacy in treating neuropathic pain.[15] FBT is indicated for use in opioid-tolerant patients, and Abraham was opioid-tolerant as a result of his daily dose of oxycodone ER (≥30 mg/d). However, his physician took the additional precaution of administering the first dose under observation. In the absence of observed adverse effects and risk factors (eg, patient history of poor adherence to medical directions, unsanctioned use of prescription depressants, use of illicit drugs or alcohol, or sleep apnea syndrome), his physician determined that the benefits of FBT in Abraham's case outweighed the risks.

Conclusion

Radiation myelopathy may be associated with chronic neuropathic pain that may be pharmacologically treated with TCAs, SNRIs, sodium channel modulators, tramadol, or opioids. Whereas baseline persistent pain may be treated with ATC analgesia, BTP, as in Abraham's case, may require additional approaches including the use of ROOs, especially for idiopathic episodes. When opioid therapy is indicated, patients should be instructed in the safe use of their medication and reassessed during the course of therapy so that the appropriate medication and dosing can be determined and the patient's QoL maximized.[16]

References

1 Katz RT. Spasticity. In. O'Young B, Young MA, Steins SA, eds. *PM&R Secrets*. Philadelphia, PA, Hanley & Belfus; 1997:487

2 Rades D, Hoskin PJ, Karstens JH, et al. Radiotherapy of metastatic spinal cord compression in very elderly patients *Int J Radiat Oncol Biol Phys.* 2007;67(1) 256-263

3 Maranzano E, Bellavita R, Floridi P, et al. Radiation-induced myelopathy in long-term surviving metastatic spinal cord compression patients after hypofractionated radiotherapy a clinical and magnetic resonance imaging analysis *Radiother Oncol* 2001,60(3):281-288.

4 Rades D, Stalpers LJA, Veninga T, Rudat V, Schulte R, Hoskin PJ Evaluation of functional outcome and local control after radiotherapy for metastatic spinal cord compression in patients with prostate cancer *J Urol* 2006, 175(2) 552-556

5. Béhin A, Delattre JY Complications of radiation therapy on the brain and spinal cord *Semin Neurol* 2004;24(4).405-417

6. Okada S, Okeda R Pathology of radiation myelopathy. *Neuropathology* 2001,21(4) 247-265

7 Genc M, Genc E, Genc BO, Kiresi DA. Significant response of radiation-induced CNS toxicity to high-dose steroid administration. *Br J Radiol.* 2006; 79(948) e196-e199.

8 Liu CY, Yim BT, Wozniak AJ Anticoagulation therapy for radiation-induced myelopathy *Ann Pharmacother.* 2001;35(2).188-191

9 Sminia P, van der Kleij AJ, Carl UM, Feldmeier JJ, Hartmann KA Prophylactic hyperbaric oxygen treatment and rat spinal cord re-irradiation. *Cancer Lett.* 2003;191(1):59-65.

10 Abrahm JL, for the ACP-ASIM End-of-Life Care Consensus Panel. Management of pain and spinal cord compression in patients with advanced cancer. *Ann Intern Med.* 1999;131(1):37-46

11. Dworkin RH, Backonja M, Rowbotham MC. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol.* 2003,60(11).1524-1534

12 Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132(3): 237-251

13. Argoff CE, Backonja MM, Belgrade MJ, et al Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain. *Mayo Clin Proc.* 2006;81(suppl 4).12-25.

14 Raja SN, Haythornthwaite JA, Pappagallo M, et al Opioids versus antidepressants in postherpetic neuralgia. a randomized, placebo-controlled trial. *Neurology* 2002,59·1015-1021

15 Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain a multicenter, randomized, double-blind, placebo-controlled study *Clin Ther* 2007;29(4):588-601

16. Fine PG. *The Diagnosis and Treatment of Breakthrough Pain.* New York, NY Oxford University Press, 2008

Chapter 9: Wendy

A Patient With Irritable Bowel Syndrome

Case

Wendy, a 25-year-old woman, has experienced frequent abdominal bloating, diarrhea, and cramping pain intermittently for the past 6 months, with pain present more than 3 days per month. Her pain is relieved by defecation, and its onset was associated with a change in the frequency of stool and increased urgency of defecation. Her PCP initially treated her symptoms as if they were related to acute viral gastroenteritis but, because they have persisted, recently referred her to a gastroenterologist. Large meals, wheat products, and caffeinated beverages all aggravate her symptoms. Eating chocolate exacerbates her abdominal symptoms, and drinking carbonated beverages increases her bloating. Wendy's symptoms also increase when she is under stress and during her menstrual period.

Current Medications

Wendy occasionally uses diphenoxylate and atropine for her diarrhea. She uses drospirenone and ethinyl estradiol for birth control.

Medical History

Wendy has occasional migraine headache with her menstrual cycle. The symptoms are episodic and not overly disabling. She has had no recent fever, weight loss or weight gain, or complaints of chest pain or shortness of breath. She has no headache complaints other than occasional migraine. She has had a tonsillectomy.

Family History

Wendy has no relevant family history.

Social History

Wendy is single and in her final year of law school. She has no history of tobacco or regular alcohol use. She occasionally drinks wine and at times notes increased abdominal symptoms when she does so. She denies recreational drug use.

Examination and Diagnosis

Wendy's gastroenterologist interviews and examines her and completes diagnostic testing; all results are normal. She is afebrile with normal vital signs (BP, 116/70 mm Hg; HR, 71 beats/min; RR, 15 breaths/min) except for her pain intensity level, which is 7/10. Her BMI, 20.2 kg/m^2, is normal. Her general examination is unremarkable. Her abdomen is not distended, but it is diffusely tender to palpation without rebound or guarding. There is no hepatosplenomegaly, a guaiac stool test is negative, and bowel sounds are present. Her neurologic examination does not demonstrate any focal findings. Diagnostic testing includes routine and specialized blood work, stool cultures, and an upper GI series with small-bowel follow-through. Wendy is given a diagnosis of IBS.

Treatment and Management

Wendy wants to know what can be done to alleviate her symptoms because at times she feels that they are overwhelming and disabling. She is concerned that she will not be able to complete law school, study for the bar examination, or practice law if she cannot be more consistently comfortable.

Wendy is given dietary advice—including recommendations to drink sufficient water, avoid legumes, and take fiber supplements—and is treated with a combination of diphenoxylate hydrochloride 2.5 mg and atropine sulfate 0.025 mg several times daily as needed. When her diarrhea and discomfort persist, she is prescribed hyoscyamine as well. When this regimen fails to alleviate her discomfort and diarrhea sufficiently, she is prescribed alosetron. This proves to be most helpful for her diarrhea, but she continues to experience significant abdominal pain. Amitriptyline is not helpful.

Her gastroenterologist refers her to a pain specialist, who recommends a trial of opioid therapy. The pain specialist emphasizes that the treatment is on a trial basis and, if successful, can be continued to help her feel more comfortable. If opioid analgesics are unsuccessful as a result of insufficient analgesia or intolerable side effects, the pain specialist stresses that other treatments can be considered.

Wendy undergoes appropriate screening before being prescribed an opioid analgesic (ORT score, 1), and she is stratified as low-risk for aberrant behaviors related to opioid use. She is told about the risks

and benefits of this therapy and signs a controlled substance agreement. Wendy is prescribed morphine ER 30 mg daily and advised to return for follow-up 1 month later. At the follow-up she reports some decrease in pain but is still uncomfortable. The pain specialist titrates her morphine ER to 60 mg daily, and then several weeks later to 90 mg daily. This dose appears to be effective, especially once augmented with a short-acting dose of morphine 15 mg taken orally 4 times daily as needed for occasional idiopathic BTP.

After Wendy has been on this regimen for 11 months, the pain specialist receives a call from Wendy's pharmacy reporting that in the last week she has attempted to fill 2 prescriptions for morphine ER—one from the pain specialist and one from another clinician. Evidently, in a behavior known as doctor shopping, Wendy has been visiting different physicians in an effort to obtain more morphine than the pain specialist has prescribed.

Upon being questioned by the pain specialist, Wendy admits that she likes the way morphine makes her feel and has been taking larger doses to experience euphoria. Despite her low initial risk for problematic behaviors related to opioid use, Wendy is clearly abusing the drug. The pain specialist explains why this is unacceptable and tells her that he is going to change the manner in which he prescribes her opioids. If she wants him to continue prescribing opioids, she will have to see him at 1-week intervals, discontinue her doctor-shopping behavior, agree to a pill count at her appointments, undergo additional, unannounced UDT, and consult with a psychologist who has expertise in addiction.

Wendy agrees to the new regimen and is able to stay on her medications without exhibiting further aberrant drug-taking behaviors. She is subsequently seen for follow-up on a monthly basis with a good outcome.

Discussion

IBS is a functional GI disorder, with a prevalence in the United States estimated to be 10% to 20% and an incidence of 1% to 2% per year.[1,2] Between 20% and 50% of referrals to a gastroenterologist involve symptoms similar to those of IBS. Approximately 20% of patients with IBS seek medical attention. Although IBS is not associated with an increased risk for mortality due to any specific medical or

other cause, the discomfort of IBS is associated with notable absenteeism from work.[3] Approximately half of patients with IBS experience the onset of symptoms, including pain, before age 35. IBS is 2 to 3 times more likely to develop in women than in men.[1] Comorbidities, such as migraine, fibromyalgia, and MDD, are common in IBS, although there is evidence of a general amplification of symptom reporting in IBS rather than unique associations.[4,5]

Several potential mechanisms of IBS have been discussed, including colonic dysmotility, smooth muscle hyperactivity, and visceral hyperalgesia.[2,6-8] Recent studies are examining the roles of microscopic amounts of inflammation and bacterial overgrowth as well.[9] Recognizing that an Axis I psychiatric disorder not only is present but often precedes the onset of GI symptoms of IBS, some authors have implicated psychopathology as a pathophysiologic mechanism of IBS.[10,11] IBS is considered a biopsychosocial disorder in which the interaction of medical and environmental factors determines how the patient experiences the illness.[12]

Patient history is the key to a diagnosis of IBS. The Manning criteria[13,14] and the Rome III criteria have been developed to help differentiate IBS from organic bowel disorders. The more recent Rome III criteria (2006),[15] which Wendy meets, require that patients have had abdominal pain at least 3 days per month during the prior 3 months, along with 2 or more of the following:

- pain relieved by defecation
- pain onset associated with a change in the frequency of stool
- pain onset associated with a change in the form or appearance of stool.

Other symptoms include mucorrhea, abdominal bloating, a subjective feeling of distention and straining, and increased urgency of defecation.[15] Certain noncolonic symptoms also have been associated with IBS (Table 1), and some symptoms are not consistent with IBS (Table 2)

Successful management of IBS is greatly enhanced by a sound patient–physician relationship.[16] Helping the patient to recognize specific stressors and develop strategies to avoid them is generally helpful.[17] IBS is a condition associated with chronic symptoms and exacerbations of which the patient needs to be aware. Any psychiatric comorbidity associated with IBS should be treated concurrently.

Table 1. Noncolonic Symptoms and Comorbid Conditions Associated With Irritable Bowel Syndrome[4]

Dyspepsia
Emesis
Fibromyalgia
Migraine headache
Nausea
Sexual dysfunction
Urinary frequency

Table 2. Symptoms Not Associated With Irritable Bowel Syndrome[14]

Fever
Gluten intolerance
Lactose or fructose intolerance
Onset in middle age or later
Painless diarrhea
Rectal bleeding
Steatorrhea
Weight loss or anorexia

Dietary changes, such as those recommended for Wendy, may also be helpful for patients.[14,16] These include adequate water intake, limited use of caffeine, fiber supplementation, and avoidance of legumes.

Various medical therapies have been proposed for the management of IBS.[17] Alosetron, which proves helpful for Wendy, is a serotonin ($5\text{-}HT_3$)–receptor antagonist that is FDA-approved for the treatment of women with severe diarrhea-predominant IBS when other, more conventional IBS treatment has not been effective (Figure 1, page 96).[18] Tegaserod has received restricted FDA approval for IBS with constipation; approval is restricted largely because of the results of a

meta-analysis of safety data pooled from 29 clinical trials of tegaserod involving more than 18,000 patients. The analysis demonstrated a significantly greater number of serious cardiovascular adverse effects (stroke, myocardial infarction, and angina) in patients taking tegaserod than in those given placebo. After being temporarily withdrawn from the market in the United States in March 2007, tegaserod became available with restrictions in July 2007.[14]

Medications without specific FDA approval for IBS that have been used to treat the symptoms associated with this condition include anticholinergic agents, such as hyoscyamine and dicyclomine, agents to reduce diarrhea, including loperamide and diphenoxylate hydrochloride 2.5 mg with atropine sulfate 0.025 mg, prokinetic agents, such as cisapride; TCAs, such as amitriptyline and imipramine (to treat the depression as well as the pain that can be associated with IBS); and agents to treat constipation, including the chloride channel activator lubiprostone and bulk-forming laxatives such as methylcellulose and psyllium.[14] Evidence-based recommendations are available for some of these agents: For example, there are insufficient data to make a recommendation about the effectiveness of hyoscyamine and dicyclomine, loperamide is not more effective than placebo at relieving

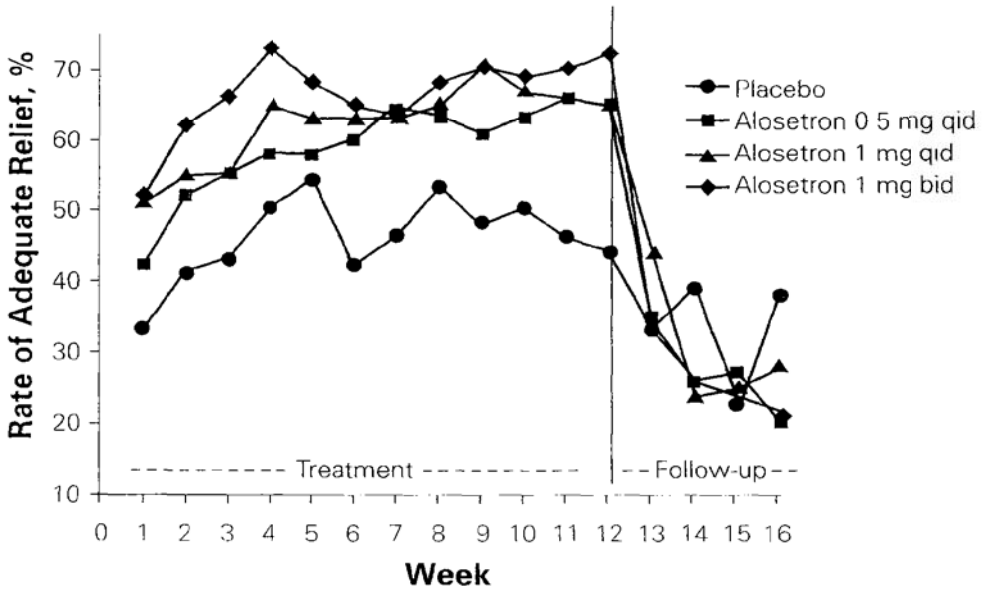


Figure 1. Relief of irritable bowel syndrome pain and discomfort with alosetron and placebo.[18]

global IBS symptoms but may be effective for diarrhea, and TCAs are not more effective than placebo at relieving global IBS symptoms but relieve abdominal pain in IBS patients [19]

Opioids can be useful in treating IBS-related pain,[20,21] although they are associated with risks, including opioid-induced bowel dysfunction, and require continuous monitoring, as in Wendy's case [22] Prescription opioid abuse is part of a larger problem of prescription drug abuse. Data collected in 2006 showed that 7 million Americans aged 12 or older used prescription-type psychotherapeutic drugs nonmedically in the past month, of these, 5.2 million used pain relievers [23] The prevalence of abuse among patients treated with opioids for chronic pain has been estimated by some to be as high as 18% to 41%, although comprehensive prospective data currently are not available [24] A strong regional correlation has been found between therapeutic exposure to opioid analgesics and abuse of those opioids, as measured by prescriptions filled.[25]

To try to minimize the risk for opioid abuse, careful risk assessment is recommended, followed by triage according to level of risk.[26] Although Wendy's score on the ORT implied low risk, the ongoing risks of opioid abuse, misuse, and diversion are dynamic and may involve the biopsychosocial stressors associated with IBS. Risk assessment tools rely on patient self-report and therefore should not be used in lieu of a comprehensive and continuous evaluation of the complete medical and social context of the individual patient. However, even when Universal Precautions are taken and patients appear to be at low risk, like Wendy, they may develop aberrant drug-taking behaviors.

These behaviors are subject to interpretation as well. Some, such as using more opioids than the physician has recommended, are believed to be less indicative of addiction, whereas others, such as Wendy's behavior of seeing 2 doctors at once without their knowledge, may be more indicative of addiction (Table 3, page 98).[27] At each visit, the physician should be alert for these behaviors, observing and nonjudgmentally questioning the patient; an instrument such as the Pain Assessment and Documentation Tool can aid in making appropriately detailed chart notes.[28] If a patient exhibits aberrant drug-taking behaviors, the physician should inquire as to the context of the behaviors. If the behavior is evidently linked to abuse, as when Wendy admits to using morphine

Table 3. Aberrant Drug-Taking Behaviors[27]

Probably More Predictive of Addiction	Probably Less Predictive of Addiction
Selling prescription drugs	Aggressively complaining about need for higher doses
Forging prescriptions	Drug hoarding during periods of reduced symptoms
Stealing or borrowing another patient's drugs	Requesting specific drugs
Injecting oral formulations	Acquiring similar drugs from other medical sources
Obtaining prescription drugs from nonmedical sources	Unsanctioned dose escalation once or twice
Concurrently abusing related illicit drugs	Unapproved use of drugs to treat another symptom
Multiple unsanctioned dose escalations	Reporting psychic effects not intended by the clinician
Recurrent losses of prescriptions	

Note: Behaviors are listed according to whether they are more or less likely to be indicative of addiction.

for euphoria, steps must be taken to address the problem. A multidisciplinary approach is recommended, such as involving a psychologist or an addiction specialist.[29] The treatment plan also may include greater structure, provided by 1- or 2-week follow-up appointments, pill counts, and UDT. With such a plan in place, even a patient with a current drug abuse problem may be able to continue receiving opioid treatment for pain. However, if the aberrant drug-taking behaviors do not decrease, the opioids may need to be tapered and the patient offered an alternative therapeutic plan.

Conclusion

IBS is a functional disorder that may result in various GI symptoms and in moderate to severe chronic pain. Ideally, successful primary therapies directed at the underlying disorder, as well as symptomatic therapies—including analgesic agents for the management of

the chronic pain associated with this disorder—can be identified to help improve the patient's QoL. When opioids are prescribed for any patient, it is important to recognize not only the potential benefits of treatment but also potential risks. To this end, proper assessment before opioid treatment and monitoring during treatment are required, along with changes in treatment structure if necessary.

References

1. Cash BD, Chey WD. Advances in the management of irritable bowel syndrome. *Curr Gastroenterol Rep*. 2003;5(6):468-475.
2. Camilleri M. Functional gastrointestinal disorders: novel insights and treatments. Medscape General Medicine. http://www.medscape.com/viewarticle/407938. Accessed December 20, 2007.
3. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology*. 1997;112(6):2120-2137.
4. Cole JA, Rothman KJ, Cabral HJ, Zhang Y, Farraye FA. Migraine, fibromyalgia, and depression among people with IBS: a prevalence study. *BMC Gastroenterol*. 2006;6:26. doi:10.1186/1471-230X-6-26.
5. Whitehead WE, Palsson OS, Levy RR, Feld AD, Turner M, Von Korff M. Comorbidity in irritable bowel syndrome. *Am J Gastroenterol*. 2007;102(12):2767–2776.
6. Kellow JE, Phillips SF, Miller LJ, et al. Dysmotility of the small intestine in irritable bowel syndrome. *Gut*. 1988;29(9):1236-1243.
7. Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. *Gastroenterology*. 1987;92(6):1885-1893.
8. Whitehead WE, Holtkotter B, Enck P, et al. Tolerance for rectosigmoid distention in irritable bowel syndrome. *Gastroenterology*. 1990;98(5):1187-1192.
9. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol*. 2000;95(12):3503-3506.
10. Walker EA, Roy-Byrne PP, Katon WJ, et al. Psychiatric illness and irritable bowel syndrome: a comparison with inflammatory bowel disease. *Am J Psychiatry*. 1990;147(12):1656-1661.
11. Miller V, Hopkins L, Whorwell PJ. Suicidal ideation in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2004;2(12):1064-1068.
12. Halpert A, Drossman D. Biopsychosocial issues in irritable bowel syndrome. *J Clin Gastroenterol*. 2005;39(8):665-669.
13. Manning AP, Thompson WG, Heaton KW, et al. Towards positive diagnosis of the irritable bowel. *Br Med J*. 1978;2(6138):653-654.

14 Lehrer JK, Lichtenstein GR. Irritable bowel syndrome. eMedicine. http://www.emedicine.com/med/TOPIC1190.HTM. Accessed December 20, 2007.

15 Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology*. 2006;130(5):1480-1491.

16 Morgan T, Robson KM. Irritable bowel syndrome. *Postgrad Med*. 2002; 112(5):30-40.

17. Spiller R. Clinical update: irritable bowel syndrome. *Lancet*. 2007;369(9573): 1586-1588.

18 Krause R, Ameen V, Gordon SH, et al. A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 mg and 1 mg alosetron in women with severe diarrhea-predominant IBS. *Am J Gastroenterol*. 2007;102(8):1709-1719.

19 American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. Evidence-based position statement on the management of irritable bowel syndrome in North America. *Am J Gastroenterol*. 2002; 97(11 suppl):S1-S5.

20 Saad RJ, Chey WD. Recent developments in the therapy of irritable bowel syndrome. *Expert Opin Investig Drugs*. 2008;17(2):117-130.

21 De Giorgio R, Barbara G, Furness JB, Tonini M. Novel therapeutic targets for enteric nervous system disorders. *Trends Pharmacol Sci*. 2007;28(9): 473-481. [published online ahead of print August 30, 2007]

22. Nicholson B, Passik SD. Management of chronic noncancer pain in the primary setting. *South Med J*. 2007;100(10):1028-1036.

23 Substance Abuse and Mental Health Services Administration. *Results from the 2006 National Survey on Drug Use and Health: National Findings*. Rockville, MD: Office of Applied Studies, NSDUH Series H-32, DHHS Publication No. SMA 07-4293, 2007.

24 Manchikanti L. Prescription drug abuse: what is being done to address this new drug epidemic? Testimony before the subcommittee on criminal justice, drug policy and human resources. *Pain Physician*. 2006;9(4):287-321.

25. Cicero TJ, Surratt H, Inciardi JA, Munoz A. Relationship between therapeutic use and abuse of opioid analgesics in rural, suburban, and urban locations in the United States. *Pharmacoepidemiol Drug Saf*. 2007;16(8): 827-840.

26. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med*. 2005;6(2): 107-112.

27 Passik SD, Kirsh KL, Donaghy KB, Portenoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clin J Pain*. 2006;22(2):173-181.

28. Passik SD, Kirsh KL, Whitcomb L, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clin Ther*. 2004;26(4):552-561.

29. Passik SD, Kirsh KL. Opioid therapy in patients with a history of substance abuse. *CNS Drugs*. 2004;18(1):13-25.

Chapter 10: Dorothy
A Patient With Fibromyalgia

Case

Dorothy, a 44-year-old woman with a history of MDD, has experienced periods of remission and relapse during the past 20 years. She has been under the care of a psychiatrist for most of that time and has been treated exclusively on an outpatient basis with medication and psychotherapy. Several weeks ago, she was riding her bicycle when she was hit by a car. She did not lose consciousness but was taken by an ambulance to the local hospital, where she was evaluated in the emergency department. She described pain in her neck and low back, so the physician ordered X-ray films of the cervical and lumbar spine, which did not show any significant structural abnormality. Dorothy was discharged with a prescription for diclofenac 75 mg orally twice daily.

Since the accident, Dorothy has begun to note increased depressive symptoms as well as generalized pain. She requests an urgent appointment with her psychiatrist to discuss these changes.

Current Medications

Dorothy reports the use of sertraline 50 mg orally daily as prescribed by her psychiatrist, as well as norgestrel and ethinyl estradiol, an oral contraceptive. Since shortly after the motor vehicle accident, when she used up her prescription for diclofenac, her widespread pain has prompted her to use OTC medications—ibuprofen 200 mg several times daily or APAP 1,000 mg several times daily.

Medical History

Dorothy has no history of hypertension, DM, asthma, migraine or other headache disorders, collagen vascular disorder, or GI disorders. She underwent an appendectomy at age 12, a lumpectomy (benign) of the right breast at age 34, and a cholecystectomy at age 37 for cholecystitis. Dorothy denies medical and environmental allergies.

Family History

Dorothy's mother and father, who are 73 years old, both receive treatment for hypertension, dyslipidemia, and mild osteoarthritis. She has 2 sisters and a brother. Her 42-year-old sister has recently been given a diagnosis of hypertension, which is responding to medical therapy, and her 37-year-old sister and 35-year-old brother have no known significant medical problems.

Social History

Dorothy is married with 2 sons, aged 5 and 7. She works full-time as an administrative assistant at a local hospital. She shares child care responsibilities with her husband. Her hobbies include biking, sewing, cooking, and knitting. She does not smoke, has an occasional glass of wine, and denies the use of recreational drugs, although she "experimented" a bit in college.

Examination and Diagnosis

No further testing has been done since the accident.

Treatment and Management

During the follow-up visit with her psychiatrist, Dorothy reports increased depressive symptoms and pain throughout her body since shortly after the biking accident. She is sleeping poorly and is concerned about concentrating sufficiently at work. She describes feeling fatigued and generally tired every day. Dorothy's psychiatrist informs her that the pain and other symptoms are likely related to an episode of worsening MDD. He increases her dose of sertraline to 100 mg daily. No diagnostic tests are ordered.

Dorothy's depression, pain, and other symptoms do not decrease with the new dose of sertraline. At her next appointment 1 month later, she reports continued generalized and severe pain rated 10/10, and she expresses concern about worsening depression. No physical examination is performed, and she is advised to continue on the same regimen and to return in another month.

Dorothy begins to miss work because of her pain, depression, and fatigue. She is considering going to an emergency room or other urgent care setting for psychiatric treatment. She no longer feels she can cope with her ADLs. While at a hair salon, she reads a magazine

article about fibromyalgia syndrome (FMS) and recognizes many of the symptoms in her own case. Dorothy calls her PCP the next day. At that appointment, the PCP takes her history, examines her, and suggests that she undergo a series of blood tests.

Dorothy's PCP finds pain at tender points bilaterally in her arms, legs, and neck, as well as in her cervical, thoracic, and lumbar regions. Her pain intensity level is rated as 8/10. He finds no other general or neurologic abnormalities. The results of screening blood tests for collagen vascular disease and other possible systemic causes of her complaints all are normal. Her physician feels confident, based on her history, examination, and laboratory results, that in addition to MDD, Dorothy's constellation of symptoms is consistent with a diagnosis of FMS. Dorothy is still worried about her level of pain and low mood but is relieved to receive a diagnosis.

After speaking with Dorothy's psychiatrist, the PCP recommends that she continue sertraline but adds pregabalin at a starting dose of 75 mg orally twice daily. This dose is raised to 150 mg twice daily after 1 week, and to 225 mg twice daily after 2 weeks. He also asks Dorothy to continue biking for aerobic exercise as often as she is able. After several weeks on the new regimen, Dorothy feels much improved and is able to resume most of her normal activities, although she notes that her pain intensity level increases to 5-6/10 after a particularly strenuous bike ride. The PCP suggests that she take 375 mg of naproxen 30 minutes before activities that might be associated with the BTP. This is successful, and at her 3-month follow-up visit, Dorothy reports her overall average pain intensity level to be 3/10, without breakthrough episodes.

Discussion

FMS is a chronic pain disorder of unknown etiology characterized by widespread pain of at least 3 months' duration in combination with pain on palpation in at least 11 of 18 specific tender points on the body.[1] Its estimated prevalence in the United States is 2% (between 4 and 6 million affected Americans), with women affected more frequently than men.[2]

Because the pathophysiology of FMS is uncertain,[3,4] reaching a diagnosis of this condition may be challenging, even to the experienced clinician. Thus, it has been considered by many to be a diagnosis of

exclusion. However, in 1990, the American College of Rheumatology issued diagnostic and classification criteria for the purpose of improving accuracy and consistency in this area.[1] Despite controversies surrounding the syndrome, FMS is now widely accepted as a chronic medical disorder. Evidence-based treatments have emerged for FMS, including an FDA-approved drug for this indication, pregabalin.

The diagnosis of FMS is complicated by numerous comorbidities. Patients with FMS are 2 to 7 times more likely to have mental illnesses, functional somatic disorders, and autoimmune disorders.[5] Dorothy has MDD, which is not unusual, an estimated 69% of patients with FMS in the United States may have this diagnosis at some point during their lifetime.[6] Other common psychiatric comorbidities of FMS include bipolar disorder, generalized anxiety disorder (GAD), eating disorders, and substance abuse disorders. Other medical conditions that occur in patients with FMS include chronic headache, chronic fatigue, restless legs syndrome, IBS, tinnitus, impaired coordination, and various skin problems.[7] Autoimmune comorbidities include systemic lupus erythematosus and rheumatoid arthritis (RA). Laboratory testing is recommended to evaluate for conditions, such as RA, that can resemble FMS.

The relationships between comorbidities and FMS are under active investigation. Recent research shows that MDD and FMS may be related by common etiologic factors, such that although there is no causal relationship, the conditions share certain risk factors, genetic or otherwise.[8] Neuroimaging studies have provided objective evidence of abnormal central regulation of pain in FMS, such as augmented brain responses to both painful and nonpainful stimuli, which may be amplified by depressed mood and catastrophizing.[9]

The coexistence of depression or anxiety in a patient with FMS may have an adverse effect on the overall management of this condition. Dorothy's experience with a delayed diagnosis is unfortunately not uncommon. The onset of FMS often follows a traumatic experience such as a motor vehicle accident.[10] Dorothy's case shows that it is important for clinicians to re-evaluate patient complaints continually and address new symptoms. Painful physical symptoms can coexist with MDD and GAD, which can in turn magnify pain levels. In Dorothy's case, the trauma of the biking accident appears to have rekindled and exacerbated her mood disorder and also triggered FMS. Any unremitting pain must be fully assessed.

A practical consideration is that health care providers are under increasing pressure to be "efficient," which can translate into a reduction in the amount of time spent with each patient. This may lead to a failure to address new complaints, particularly in patients with persistent pain, for whom making a diagnosis can be difficult and time-consuming. Even if the psychiatrist was responding appropriately initially, the fact that Dorothy's pain was not decreasing despite psychopharmacologic intervention suggested that further evaluation was necessary. For Dorothy, a referral back to her PCP, who would have been familiar with her medical history, would probably have been most appropriate. At that juncture, the PCP could have determined his or her familiarity with the syndrome and its treatment and proceeded with additional consultations as needed.

There is no pathognomonic diagnostic test for FMS. The *Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children* lists recommendations for assessment and diagnosis (Table 1 and Figure 1, pages 106 and 107).[1,11-13] MRI of the neck may be used to exclude anatomic lesions that can cause pain, but in the absence of specific neurologic signs (eg, sensory or motor deficits), this is a "low-yield" procedure. A rheumatologist may be consulted to exclude RA or other underlying collagen vascular or inflammatory disease, and a neurologist may be asked to help exclude neurologic disorders that are characterized by symptoms that can mimic those of FMS.

Nonpharmacologic treatments for FMS with good evidence of efficacy include exercise, heated pool treatment, and CBT.[14-16] Because Dorothy already had an active hobby, bicycling was a natural choice for regular aerobic exercise. With appropriate treatment for pain, she was able to resume and even increase her participation in this activity.

The American Pain Society and the European League Against Rheumatism separately have developed evidence-based pharmacologic recommendations that do not completely overlap (in part because they were developed at different times).[11,14] Together, these recommendations include tramadol (for pain), TCAs (eg, amitriptyline or cyclobenzaprine [usually referred to as a muscle relaxant although it has a tricyclic structure] to improve sleep and mood), selective serotonin reuptake inhibitors (SSRIs; eg, fluoxetine), and SNRIs (eg, duloxetine).[12,13] Milnacipran, an SNRI, is also included in the European guidelines, but it is not available in the United States.

Table 1. Diagnosis and Assessment of Fibromyalgia Syndrome[11]

1. Begin the evaluation of a patient with suspected FMS with a complete history and physical examination. The examiner should focus on illnesses that may mimic or complicate FMS, such as hypothyroidism and ankylosing spondylitis, or that can occur concurrently with FMS, such as tendonitis, systemic lupus erythematosus, rheumatoid arthritis, and osteoarthritis. The clinician should perform a complete joint examination, manual testing of muscle strength, and a neurologic examination.
2. Base the clinical diagnosis of FMS on the presence of widespread pain, defined as pain in all 4 body quadrants and axial pain, for at least 3 consecutive months. The only physical examination criterion for the diagnosis of FMS is the presence of excess tenderness to manual palpation at a minimum of 11 of 18 muscle–tendon sites noted during the manual tender point examination.
3. Focus the assessment of pain on its type and quality, source, location, duration, time course, pain affect, and effects on QoL. Use the patient's self-report as the primary basis of the pain assessment, and use the same pain measurement tool at subsequent visits.
4. Evaluate the severity of other FMS symptoms, including fatigue, sleep disturbance, and mood and cognitive disturbance. Refer people with suspected mood disorders for formal psychological testing.
5. Assess functional status at the initial and subsequent patient visits. Measure the impact of FMS on physical and emotional function and overall QoL.
6. Obtain a complete blood cell count and measurements of the erythrocyte sedimentation rate, muscle enzymes, liver function, and thyroid function in a new patient with probable FMS.

FMS, fibromyalgia syndrome, **QoL,** quality of life

The only FDA-approved medication for FMS is pregabalin. In an 8-week randomized, double-blind, placebo-controlled trial completed by 410 patients with FMS, pregabalin at 450 mg per day significantly reduced the average severity of pain in the primary analysis compared with placebo (–0.93 on a scale of 0-10; $P \leq 0.001$).[17] Significantly more patients who received 450 mg of pregabalin per day had a reduction of 50% or more in pain (29% vs 13% in the placebo group; $P=0.003$). This dose of pregabalin was also associated with improved

health-related QoL. Common adverse events (>10%) included dizziness, somnolence, headache, dry mouth, and peripheral edema. In a 32-week study evaluating 1,051 adults with FMS, pregabalin had a longer time to loss of therapeutic response than placebo ($P<0.0001$); more than half of the pregabalin group had not lost response by trial end.[18] Pregabalin demonstrated durability of effect for maintaining decreased pain associated with FMS.

Dorothy's treatment strategy, combining the SSRI sertraline and the $\alpha_2\delta$ ligand pregabalin, addressed her FMS as well as her MDD.[19] Published data from controlled clinical trials suggest that duloxetine also may be effective for both of these disorders.[20]

Corticosteroids are considered inappropriate for FMS, as are μ-opioid receptor agonists (in contrast to the mixed-mechanism agent tramadol) because of inefficacy and long-term side effects, including concerns about lowering pain tolerance and inducing hyperalgesia.[11] Moreover, NSAIDs should not be used as the primary pain medication, especially long term, because they have been shown to be ineffective when used alone and are associated with GI and cardiovascular risks.[21]

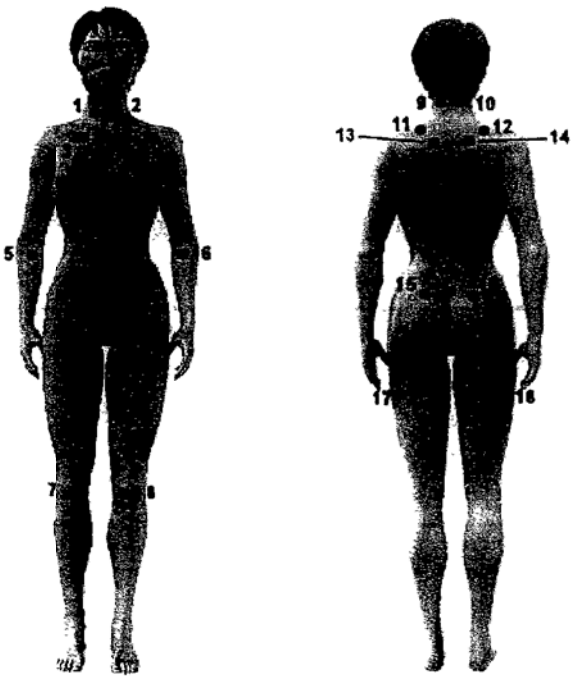


Figure 1. Fibromyalgia tender points.[1]

Conclusion

FMS is challenging to recognize and manage, but published guidelines are available and practitioners should be familiar with them to make apt diagnoses and management decisions. In FMS and all chronic pain conditions, assessment should be thorough and tailored to each patient's circumstances, with attention paid to past medical history, social and family history, ongoing underlying conditions, pain descriptors, interference with QoL, physical examination findings, and pertinent diagnostic testing. As in Dorothy's case, chronic pain conditions often are comorbid with other medical and psychiatric disorders that can complicate diagnosis and treatment; clinicians should be aware of the common comorbidities and assess and treat them in the context of overall patient management.

Chronic pain often exhibits 2 temporal patterns, baseline persistent pain and BTP, both of which should be treated. Clinicians should also be aware that patients with chronic pain may require treatment by a multidisciplinary health care team, including the patient's PCP and additional specialists as indicated.

References

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. *Arthritis Rheum.* 1990;33(2):160-172.
2. Wolfe F, Ross K, Anderson J, Russell IJ, Hiebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum.* 1995;38(1):19-28.
3. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of fibromyalgia. *Ann Intern Med.* 2007;146(10):726-734.
4. Vierck CJ Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain.* 2006;124(3):242-263
5. 5 Weir PT, Harlan GA, Nkoy FL, et al. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. *J Clin Rheumatol.* 2006;12(3):124-128
6. Epstein SA, Kay G, Clauw D, et al. Psychiatric disorders in patients with fibromyalgia. A multicenter investigation. *Psychosomatics.* 1999;40(1):57-63.
7. Chakrabarty S, Zoorob R. Fibromyalgia. *Am Fam Physician.* 2007;76(2):247-254.

8. Raphael KG, Janal MN, Nayak S, Schwartz JE, Gallagher RM. Familial aggregation of depression in fibromyalgia: a community-based test of alternate hypotheses. *Pain*. 2004;110(1-2):449-460.

9. Cook DB, Stegner AJ, McLoughlin MJ. Imaging pain of fibromyalgia. *Curr Pain Headache Rep*. 2007;11(3):190-200.

10. Al-Allaf AW, Dunbar KL, Hallum NS, et al. A case-control study examining the role of physical trauma in the onset of fibromyalgia syndrome. *Rheumatology (Oxford)*. 2002;41(4):450-453.

11. Burckhardt CS, Goldenberg D, Crofford L, et al. *Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children*. American Pain Society Clinical Practice Guideline Series. Glenview, IL: American Pain Society; 2005.

12. Okifuji A, Turk DC, Sinclair JD, Starz TW, Marcus DA. A standardized manual tender point survey: I. Development and determination of a threshold point for the identification of positive tender points in fibromyalgia syndrome. *J Rheumatol*. 1997;24(2):377-383.

13. Fibromyalgia symptoms. http://www.fibromyalgia-symptoms.org/fibromyalgia_diagnosis.html. Accessed January 23, 2008.

14. Carville SF, Arendt-Nielsen S, Bliddal H, et al. EULAR evidence based recommendations for the management of fibromyalgia syndrome [published online ahead of print October 3, 2007]. *Ann Rheum Dis*. 2008;67(4):536-541.

15. Sarzi-Puttini P, Buskila D, Carrabba M, Doria A, Atzeni F. Treatment strategy in fibromyalgia syndrome: where are we now? *Semin Arthritis Rheum*. 2007 Oct 30 [Epub ahead of print].

16. Burckhardt CS. Nonpharmacologic management strategies in fibromyalgia. *Rheum Dis Clin North Am*. 2002;28(2):291-304.

17. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2005;52(4):1264-1273.

18. Crofford LJ, Mease PJ, Simpson SL, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): A 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain*. 2008 Apr 7 [Epub ahead of print].

19. Maizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic non-cancer pain. *Am Fam Physician*. 2005;71(3):483-490.

20. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum*. 2004;50(9):2974-2984.

21. Yunus MB, Masi AT, Aldag JC. Short-term effects of ibuprofen in primary fibromyalgia syndrome: a double blind, placebo controlled trial [published correction appears in *J Rheumatol* 1989;16(6):855]. *J Rheumatol*. 1989;16(4):527-532.

NOTES

CME Post-Test

1. **Which of the following is not a recognized subtype of breakthrough pain (BTP)?**
   a. Idiopathic
   b. Occasional
   c. Precipitated/incident
   d. End-of-dose failure

2. **The use of validated neuropathic pain rating scales _____.**
   a. can help differentiate between neuropathic and non-neuropathic pain states
   b. is not recommended in the assessment of chronic pain
   c. obviates the need for a physical examination
   d. cannot help clarify the pathophysiology of chronic pain

3. **Appropriate strategies to address end-of-dose failure include _____.**
   a. increasing the dosing interval
   b. switching to a longer-acting drug formulation
   c. decreasing the baseline dose
   d. all of the above

4. **Which of the following tools can help the clinician assess a patient's risk for opioid abuse?**
   a. Brief Pain Inventory
   b. Opioid Dose Conversion Calculator
   c. Screener and Opioid Assessment for Patients with Pain-Revised Version
   d. None of the above

5. **Which of the following are included in the 4 A's for ongoing monitoring of patients with chronic pain?**
   a. Adverse events and aberrant behaviors
   b. Activities of daily living and adjuvant medications
   c. Access to medication and addiction
   d. Analgesia and access to medications

6. **Common adverse events associated with opioids include _____.**
   a. constipation

b. pruritus
c. somnolence
d. all of the above

7. **Multidrug strategies may be advantageous because they _____.**
a. are never associated with adverse events
b. allow clinicians to use higher opioid doses
c. can target multiple sites along pain signaling pathways
d. prevent diversion of opioid medications

8. **Osteoarthritis is _____.**
a. characterized by degeneration of bone only
b. often associated with pain resulting from inflammation, microfractures in subchondral bone, and/or osteophytes
c. not associated with aging
d. relatively uncommon in most Western countries

9. **A concern in prescribing capsaicin as a topical analgesic for osteoarthritis pain is _____.**
a. hepatic and renal toxicity
b. increased pain upon application to the skin
c. upper gastrointestinal complications
d. respiratory depression

10. **Among patients with pancreatic cancer, what proportion report pain on initial presentation?**
a. 5% to 10%
b. 30% to 35%
c. 40% to 45%
d. 75% to 80%

11. **When prescribing a rapid-onset opioid for cancer-related BTP, the clinician should _____.**
a. begin with 40% of the baseline opioid dose
b. ensure that the patient is being treated with fentanyl for baseline pain
c. confirm that the patient is opioid-tolerant
d. all of the above

CME Post-Test

12. Which of the following statements is false?

a. The effective dose of fentanyl buccal tablet (FBT) is proportional to the daily opioid dose used to treat baseline pain.
b. FBT has a higher absolute bioavailability than oral transmucosal fentanyl citrate (OTFC).
c. FBT and OTFC are FDA-approved for cancer-related BTP.
d. A Cochrane Collaboration Review showed that OTFC was superior to placebo, immediate-release morphine, and patients' previous rescue medications for the treatment of BTP.

13. Which of the following can be a cause of lumbar facet arthropathy?

a. Rheumatoid arthritis
b. Small fractures from recurrent trauma
c. Osteoarthritis
d. All of the above

14. Which of the following statements is true?

a. Exercise and massage have proved beneficial in relieving back pain symptoms.
b. Opioids are not commonly prescribed for low back pain (LBP).
c. LBP treatment approaches based on a single modality have shown higher success rates than have multidisciplinary treatment strategies.
d. Patients with LBP who are treated with opioids almost never display aberrant drug-taking behaviors.

15. Which of the following situations may require discontinuation of opioid-based treatment for LBP?

a. Insufficient gains in analgesia and function
b. Intolerable adverse events
c. Noncompliance with treatment agreements
d. All of the above

16. Complex regional pain syndrome generally occurs _____.

a. after some degree of physical trauma
b. more commonly in men than women
c. in the absence of nerve damage
d. with a clear pathophysiology

17. **Which of the following statements about pseudoaddiction is not true?**
    a. Patient behaviors may be identical to those observed in patients with addiction.
    b. It can be diagnosed by determining the patient's response to adequate analgesia.
    c. It suggests that the patient is overmedicated.
    d. When pain relief improves, aberrant drug-taking behaviors resolve.

18. **Which of these statements about the assessment of diabetic peripheral neuropathic pain (DPNP) is not true?**
    a. Patients may describe burning, sharp pain, or tingling in their feet.
    b. Symmetric distribution of pain beginning in the distal extremities and radiating upward is consistent with DPNP.
    c. If ankle reflexes are absent, the diagnosis of DPNP cannot be made.
    d. Pain assessment instruments may aid in the evaluation of patients with DPNP.

19. **Which of the following may delay the onset of complications of diabetes mellitus, including DPNP?**
    a. Prophylactic treatment with tricyclic antidepressants (TCAs)
    b. Proper treatment of hyperglycemia
    c. Preventive treatment with opioids
    d. All of the above

20. **One of the agents approved by the FDA for the treatment of painful diabetic neuropathy is _____.**
    a. tramadol
    b. lamotrigine
    c. oxycodone
    d. gabapentin

21. **Osteoporosis is characterized by _____.**
    a. a reduction in bone mass
    b. deterioration of bone microarchitecture
    c. an increased risk for fracture
    d. all of the above

CME Post-Test

22. **Appropriate initial options for the management of an acute painful vertebral fracture related to osteoporosis do not include _____.**
    a. capsaicin
    b. nonsteroidal anti-inflammatory drugs
    c. calcitonin
    d. opioids

23. **Pain due to myelopathy is a form of _____.**
    a. nociceptive pain
    b. central neuropathic pain
    c. peripheral neuropathic pain
    d. pain that cannot be induced by radiation

24. **Which statement is not true?**
    a. TCAs and serotonin norepinephrine reuptake inhibitors may be useful for treating neuropathic pain.
    b. Several guidelines have been published for the treatment of neuropathic pain.
    c. Opioids have proved to be ineffective in the treatment of neuropathic pain.
    d. Sodium channel modulators may be useful in treating neuropathic pain.

25. **In a patient with suspected irritable bowel syndrome (IBS), tests that may help exclude other disorders associated with similar symptomology include all of the following except _____.**
    a. testing for occult blood
    b. breath testing to screen for lactose and/or fructose intolerance
    c. a ferritin test
    d. microbiological studies of the stool

26. **Dietary changes that may help patients with IBS include _____.**
    a. decreased water intake
    b. fiber avoidance
    c. increased legume consumption
    d. limited use of caffeine

27. Which patient behavior is more predictive of addiction than the others?

a. Requesting specific drugs
b. Obtaining prescription drugs from nonmedical sources
c. Increasing the dose of opioids without consulting the prescribing physician
d. Drug hoarding during times of reduced symptoms

28. Which of the following is not true of fibromyalgia syndrome (FMS)?

a. It is characterized by diffuse musculoskeletal system soft tissue pain.
b. It affects men more frequently than women.
c. It cannot be traced to a specific structural or inflammatory cause.
d. Its diagnosis is often complicated by comorbidities.

29. Which of the following statements is true?

a. There is no pathognomonic diagnostic test for FMS.
b. The estimated prevalence of FMS in the United States is 15%.
c. Patients with FMS rarely have major depressive disorder.
d. Only pharmacologic therapies have shown efficacy in treating FMS.

30. Which of the following drugs is FDA-approved for fibromyalgia?

a. Milnacipran
b. Tramadol
c. Pregabalin
d. Morphine

Answer Sheet and Evaluation

Persistent and Breakthrough Pain

Date of Release June 30, 2008 Date of Expiration June 30, 2009

In order to receive credit, participants must complete the self-report credit form, post-test answer section, and activity evaluation either by mail or online

For mailed submissions, send the completed self-report credit form, post-test answer section, and activity evaluation on pages 118 through 120 to CME & Compliance, Advanced Strategies in Medicine, 545 West 45th Street, 8th Floor, New York, NY 10036 Certificates will be mailed in approximately 6 to 8 weeks after receipt of mailed submissions and verification of a passing grade

For online submissions at CMEZone com (availability may be delayed from original print date), enter the project number "CB07001" in the keyword field to directly access this activity Upon participants' passing the activity, a certificate will be displayed on screen that participants can print and keep for their records One retake is allowed.

Self-Report Credit Form (Please Print)

_____
Last Name, First Name, Middle Initial

_____
Degree

Are you a physician? (circle one) Yes No

_____
Specialty

_____
Address 1

_____
Address 2

_____
City/State/Zip+4 Code

_____ _____
Phone Fax

_____ _____
AMA Membership # or State License #

_____
E-mail Address

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of *3.0 AMA PRA Category 1 Credits*™ Physicians should only claim credit commensurate with the extent of their participation in the activity

I attest that I have spent _____ hours and _____ minutes completing this CME activity.

Signature (required)_____ Date_____

Answer Sheet and Evaluation

Post-Test Answer Section

Directions Please circle the correct answer for each question (Physicians must score at least 70% in order to receive credit.)

1.	a	b	c	d	11.	a	b	c	d	21.	a	b	c	d
2.	a	b	c	d	12.	a	b	c	d	22.	a	b	c	d
3.	a	b	c	d	13.	a	b	c	d	23.	a	b	c	d
4.	a	b	c	d	14.	a	b	c	d	24.	a	b	c	d
5.	a	b	c	d	15.	a	b	c	d	25.	a	b	c	d
6.	a	b	c	d	16.	a	b	c	d	26.	a	b	c	d
7.	a	b	c	d	17.	a	b	c	d	27.	a	b	c	d
8.	a	b	c	d	18.	a	b	c	d	28.	a	b	c	d
9.	a	b	c	d	19.	a	b	c	d	29.	a	b	c	d
10.	a	b	c	d	20.	a	b	c	d	30.	a	b	c	d

Activity Evaluation

How did you hear about this course?

❑ Brochure ❑ Colleague

❑ Internet ❑ Other (please specify)_____

This course met the following objectives:	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Distinguish the clinical characteristics of different underlying etiologies of chronic pain.	❑	❑	❑	❑	❑
Describe the temporal characteristics and treatment challenges of baseline persistent pain and breakthrough pain.	❑	❑	❑	❑	❑
Explain why and how the treatment of chronic pain must be tailored to the individual patient's underlying pain disorder, functional goals, and treatment response.	❑	❑	❑	❑	❑
Identify types of analgesics and their clinical uses, including long-acting, short-acting, and rapid-onset opioids.	❑	❑	❑	❑	❑
Implement risk assessment and risk management strategies in patients receiving opioid analgesic therapy.	❑	❑	❑	❑	❑

Will you change your practice in any way as a result of participating in this program?

❑ Yes ❑ No

If yes, please specify _____

_____

_____

Do you feel the activity was objective, balanced, and free of commercial bias?

Answer Sheet and Evaluation

❑ Yes ❑ No

If no, please specify _____

_____

_____

If presented, were discussions on off-label drugs and/or devices properly disclosed?

❑ Yes ❑ No

If no, please specify _____

_____

_____

	Poor	Fair	Good	Very Good	Excellent
Overall evaluation	❑	❑	❑	❑	❑
Course content	❑	❑	❑	❑	❑
Usefulness	❑	❑	❑	❑	❑

Additional comments: _____

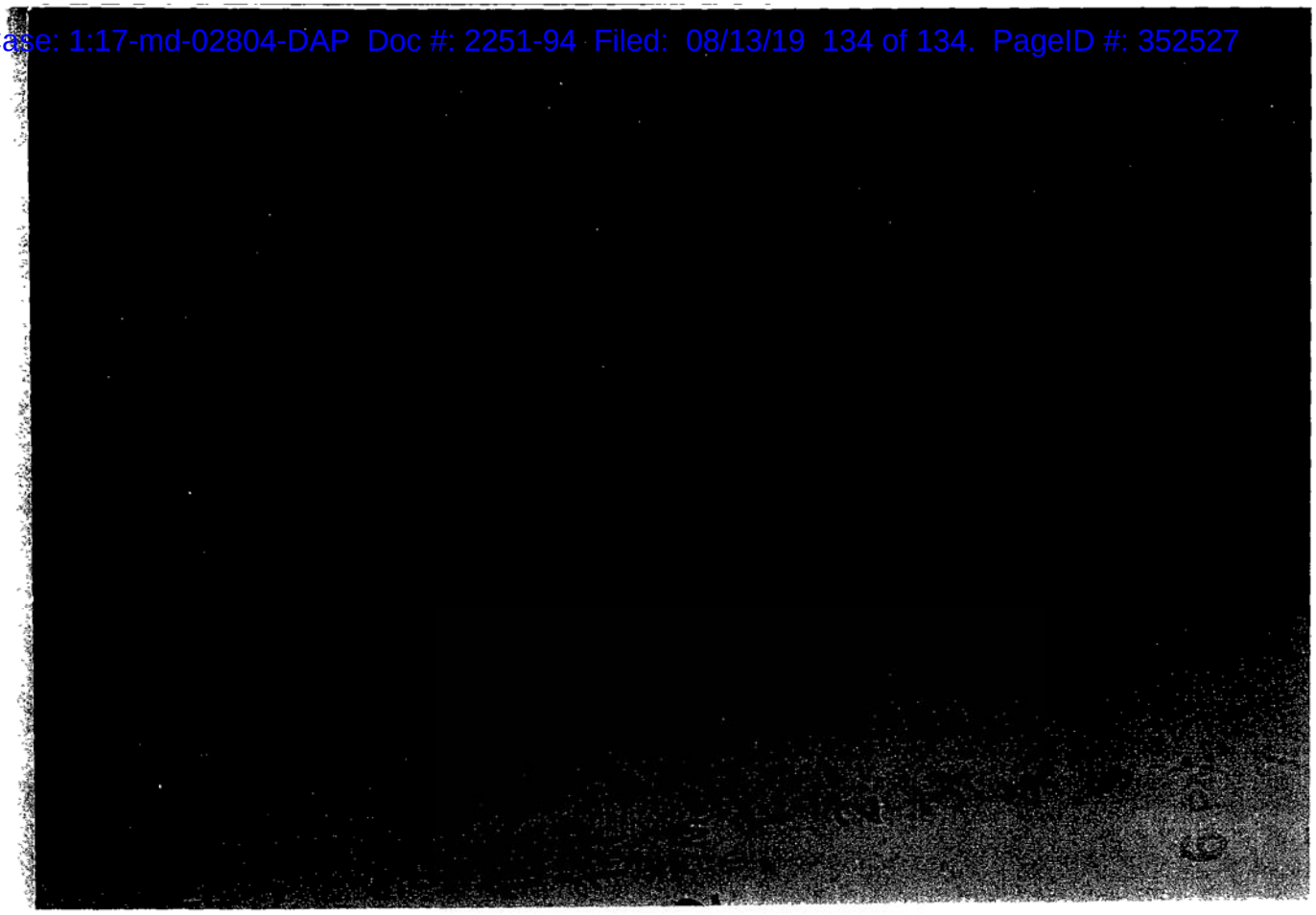
_____

_____

_____

_____

CB07001



ADVANCED STRATEGIES IN MEDICINE
A McMahon Group Company
545 West 45th Street
New York, NY 10036

CB07001